CANCER CONTROL 2017

CANCER CARE IN EMERGING HEALTH SYSTEMS

Photo: World Child Cancer

EDITOR-IN-CHIEF: **DR IAN MAGRATH**, PRESIDENT, INTERNATIONAL NETWORK FOR CANCER TREATMENT AND RESEARCH

SURVEY • CANCER CONTROL ISSUES • CERVICAL CANCER
REGIONAL INITIATIVES • PAEDIATRIC CANCER • INCTR

INCTR

PUBLISHED IN OFFICIAL ASSOCIATION WITH THE INTERNATIONAL NETWORK FOR CANCER TREATMENT AND RESEARCH

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PAEDIATRIC CANCER

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WELCOME TO THE FIFTH EDITION OF CANCER CONTROL

Cancer control 2017 is the fifth edition of our annual publication published with the International Network for Cancer Treatment and Research. This year we are pleased to have an article from the Access to Medicines Index, an NGO established in The Netherlands by the United Kingdom and Dutch Governments with help from the Bill & Melinda gates Foundation. The Index has been working for ten years to analyze how well pharmaceutical companies are managing access to their medicines for low- and middle-income countries. For the first time, cancer drugs will be incorporated into the 2018 Index. The article explains the challenges involved in this process and how access can take many forms which need evaluation.

A special focus of *Cancer Control 2017* is cervical cancer. We begin with the annual *Cancer Control* survey which asks readers to comment on "What are the priority needs for controlling HPV infection in your country? We received answers from 18 countries across the world and response ranged from improvements in raising public awareness and education to the need for more effective vaccination plans. Interestingly, some countries said it was not a priority at all as they faced greater priorities or had low incidences of cervical cancer.

We follow up the survey with some practical examples from Africa on how the treatment of cervical cancer can be improved. From the Cervical Cancer Prevention Program in Zambia we read how to create a prevention programme from scratch with very few resources and their experiences take resourcefulness in every sphere, including the psychological, to inspiring new levels. The WAKA (Wanavyama wa Kudhibiti ya HPV or Partners in controlling HPV) network uses carefully structured collaborations, both within Africa and in Europe, to share and coordinate knowledge, improve capacity and develop research, as well as lobbying local and Federal governments. Pink Ribbon Red Ribbon, based in the United States, seeks to strengthen the prevention and cure of cervical cancer by leveraging existing resources. A team working in Malawi provides more insights into how testing for cervical cancer can be improved and the positive economic impact this can have.

In other sections, the UICC explain the importance of their 2017 cancer resolution as we approach the UN High-Level Meeting on NCDs in 2018. We have an update from the prizing-winning CONCORD global cancer surveillance project and its future plans. There are regional initiative reports from the Caribbean, the Commonwealth and on the treatment of breast cancer in sub-Saharan Africa, as well as two articles describing developments in aspects of paediatric cancer.

Therefore, there is much to read and we very much hope you enjoy this edition of *Cancer Control*. We would be delighted to have your feedback and suggestions. *Cancer Control 2017* can be accessed online at **www.cancercontrol.info** together with the five previous editions. You can also find information about INCTR and its programmes, as well as details on how to join. ■

Dr Ian Magrath, Editor-in-Chief, Cancer Control and President, INCTR

Tim Probart, Publisher, Cancer Control and Global Health dynamics

CANCER CONTROL 2017 SURVEY: WHAT ARE THE PRIORITY NEEDS FOR CONTROLLING HPV INFECTION IN YOUR COUNTRY?

We asked a selection of *Cancer Control* readers around the world to give their considered opinions on what are the prority needs for controlling HPV infection in their countries? Their responses are shown below by geographical region.

AFRICA

DEMOCRATIC REPUBLIC OF CONGO: Dr Alex Mutombo, University of Kinshasa

"In the DRC, the true burden of HPV infection is underestimated due to the lack of organized screening and valid cancer registry. We must emphasize primary and secondary prevention, raise awareness of the population on HPV consequences and determine the circulating HPV strains in order to implement the appropriate HPV vaccination programme."

KENYA: David Makumi, Chairman, Kenya Network of Cancer Organizations (KENCO)

"This year Kenya has submitted a funding proposal to GAVI for a national roll out of HPV vaccinations in 2018. This proposal has a government commitment to co-fund. With nearly 5,000 new cervical cancer diagnosed annually, a national HPV vaccination programme will be a game-changer in reducing incidence."

SOUTH AFRICA: Professor Lynette Denny, Groote Schuur Hospital, Cape Town

"Putting HPV infection on the public health agenda to ensure that society understands the strong association of HPV with morbidity and mortality, that HPV is not only costly to the individual but to society as a whole. The association with stigma as well as life threatening cancers need to be emphasized."

SWAZILAND: Dr Qhing Qhing Dlamini, Public Health Specialist

"Cervical cancer is the leading cancer amongst women aged 15–44 years in Swaziland. A report on cases of cancer in Swaziland (2014–2016) presents cervical cancer as the leading cancer with 720 cases (31.1%). Approximately 280 women were diagnosed with cervical cancer in 2016, of which 110 died of the disease. Malignant neoplasm of the cervix is the most common cause of cancer-related admission in women and most referrals to South Africa are due to cervical cancer lesions. Swaziland has the highest HIV prevalence in the world, 26% for the reproductive age group (15–49 years) and women are the most affected population groups at 20%. The Ministry of Health (MOH), Swaziland plans to introduce HPV vaccination in 2018. A HPV vaccine introduction plan has been developed and costed with technical support from WHO and UNICEF. Key MOH programmes involved are EPI, SRH/Adolescent Health, School Health, NCD and Cancer Registry and the Ministry of Education Career Guidance Unit. The target group for Primary Prevention is girls 9–14 years, two doses of HPV vaccine spaced six months apart. The country may have to consider vaccinating HIV+ girls with three doses. The biggest challenge foreseen is the excessively high cost of the HPV vaccine, otherwise Swaziland is fully committed to HPV vaccine prevention."

UGANDA: Dr Robert Lukande, Department of Pathology, College of Health Sciences, Makerere University, Kampala

"In its strategic plan for cervical cancer prevention and control, Uganda, prioritizes behaviour change and vaccination against human papilloma virus (HPV) infection. The priority needs include programme roll out and monitoring, ensuring adequate vaccine stock, ensuring cold chain space, training health workers and updating the health management information system (HMIS) to include HPV vaccination data."

ZIMBABWE: Anna Mary Nyakabau

"Priority for controlling HPV infection in Zimbabwe

includes focus on preventive part of comprehensive control. Raising awareness through education and health promotion and integration of HPV control into HIV/AIDS programmes is cost-effective and sustainable. Preventive HPV vaccine should cover HPV strains causing cervical cancer and genital warts."

ASIA

THE PHILIPPINES: Dr Jimmy A Billod, Consultant, Section of Gynecologic Oncology, Baguio General Hospital and Medical Centre

"I believe that one of weakest links is information dissemination regarding HPV infection, and one of the priorities is to strengthen the information dissemination programmes of the DoH, collaborating with private and public health sectors as well as with the medical societies. Information drives should not only involve women but men as well. It should be inculcated in education and in all strata of employment. The dissemination initiatives must be active and done regularly and not just print ads."

CENTRAL ASIA

KAZAKHSTAN: Dr Dilyara Kaidarova, Director of Kazakh Research Institute of Oncology and Radiologyand Academician, Kazakh National Academy of Sciences

"Cervical cancer is the second most frequent cancer after breast cancer in women in Kazakhstan with an estimated 1,700 new cases in 2016. Cytology-based cervical cancer screening was introduced in 2008. The implementation of PAP smears has increased the detection of cervical cancer between 2008 and 2016, from 15.6 to 19.1 per 100,000 population. Despite the improvement in the quality of screening, the introduction of liquid-based cytology in 2011 and improvements in the quality of treatment, mortality from cervical cancer remains quite high (7.1 per 100,000 in 2016) due to high levels of detectability at the late stage. The existing screening programme needs to be improved through the introduction of HPV testing for those at high-risk and HPV vaccination for adolescent girls."

EASTERN EUROPE

BULGARIA: Dr Petar P Grozdanov, Head, Laboratory Centre Pasteur, The Stephan Angeloff Institute of Microbiology, Bulgarian Academy of Sciences, Sofia

"Despite the considerable success registered by the early detection procedures for cervical cancer prevention, cervical screening seems to benefit only a minor part of Bulgarian female population. Organized screening programmes with high population coverage must become a major priority for controlling HPV infection in Bulgaria. Importantly, organized screening programmes can have a very large and immediate impact in reducing cervix cancer rates. There is a need for age-group-targeted interventions and specific policy programmes to eliminate the remaining inequalities."

RUSSIAN FEDERATION: Professor Svetlana Rogovskaya, President, RAGIN (Russian Association for Genital infections and Neoplasia) and Professor, Federal Russian Medical Academy of Postgraduate Education (RMANPO)

"Our country is too big to make the answer simple. But the system of public healthcare is improving currently (I hope). Our women have the opportunity to get free care but the coverage for screening is low. The screening is opportunistic. I think that the priority needs are education and informing our women that they can receive a Pap-test every year for free; the HPV test is widely available but costs money. Our Association is involved in the educational and research process. For our publications see www.rmapo,ru."

LATIN AMERICA

ARGENTINA: Dr Silvina Arrossi, Scientific Coordinator, National Programme on Cervical Cancer Prevention, National Cancer Institute

"Priority needs are assuring HPV vaccination of girls and at least once in a lifetime HPV screening for all women aged 30 and over."

BELIZE: Laura Tucker-Longsworth, OBE: Speaker, National Assembly of Belize and President, Belize Cancer Society

"Continuous public education on HPV vaccine, and the "screen and treat" method is high priority for the control of HPV infection and cervical cancer in Belize. The Ministry of Health introduced the HPV vaccine into the national vaccination schedule in 2016. Vaccinated, unexposed girls will be protected against cervical cancer caused by HPV types 16, 18 and genital warts. Strong partnerships and intense dialogue with targeted groups proved to be the key to successful launch of the HPV vaccine in primary schools with 58% coverage at the introductory phase."

CHILE: Claudio Villota, Fundación Ciencia & Vida – Andes Biotechnologies SpA and Departamento de Ciencias Químicas y Biológicas, Facultad de Salud, Universidad Bernardo O'Higgins, Santiago and Jaime Villegas, Fundación Ciencia & Vida – Andes Biotechnologies SpA and Facultad de Ciencias Biológicas, Universidad Andrés Bello

"First, carry out public campaigns to inform the public that

cervical cancer can be prevented with adequate sexual behaviour. A strong educational policy of public health about sexual transmitted diseases. Application of HPV vaccine programme for girls in schools. A strong programme focus in the early detection of cervical lesions."

MEXICO: Dr Elsa Dias Lopez Obstetrician and Gynaecologist, Mexico City

"In Mexico, people need education in sexual transmitted infections to show the impact of HPV and the diseases associated with HPV; an increase in the coverage of vaccination in men and older people of both genders to show the need for protection although they have already started having sexual intercourse and scientific evidence about the security and efficacy of all vaccines against HPV. Many of the people do not know this and the social networks underestimate the advantages of vaccination."

MIDDLE EAST

EGYPT: Professor Hussein Khaled, Cairo

"Control of HPV infection is not a priority in Egypt for many reasons: firstly HCV infection is currently the most important priority as it causes hepato cellular carcinoma which is the most common cancer in Egypt according to our national cancer registry. Secondly, cervical cancer is not frequent among Egyptian females, and thirdly other sequelea of HPV infection are not important health problems here."

IRAN: Professor Reza Malekzadeh, Tehran University of Medical Sciences, Shariati Hospital, Tehran

"HPV infection control at the present time is not a priority in Iran but it should become a priority in future."

SOUTH ASIA

BANGLADESH: Professor Ashrafun Nessa, Bangabandhu Sheikh Mujib Medical University, Dhaka

"Cervical cancer can be prevented and controlled through a combined strategy of vaccinating adolescent girls against HPV and implementing population-based cervical cancer screening by HPV testing and treatment of cervical precancer and cancer. GOB completed a HPV vaccine demonstration programme for girls of grade V at school and 10 years at community."

INDIA: Dr R A Badwe, Director, ACTREC (Advanced Centre for Treatment, Research and Education in Cancer), Navi, Mumbai

"The priority in India is not to control an infection that is common but leads to serious illness in only a very small minority of infected individuals – it is to diagnose invasive cervical cancers in women early and deliver standard treatment that will result in highest chance of cure."

CANCER CONTROL ISSUES

CANCER RESOLUTION 2017: DRIVING NATIONAL ACTION IN THE COUNTDOWN TO 2025

REBECCA MORTON DOHERTY (TOP LEFT), HEAD, CITY ENGAGEMENT AND IMPACT, C/CAN 2025: CITY CANCER CHALLENGE, UICC; **MICAELA NEUMANN** (TOP RIGHT), ADVOCACY MANAGER, UICC AND **DR JULIE TORODE** (BOTTOM LEFT), DEPUTY CEO AND ADVOCACY AND NETWORKS DIRECTOR, UICC, GENEVA, SWITZERLAND



In May 2017, the cancer community celebrated a landmark achievement with the adoption of a new resolution on cancer, providing a health systems response to cancer that can accelerate progress towards the 2025 targets for reducing premature cancer deaths. Helping countries to prioritize limited resources and refocus efforts between now and 2025, and more immediately in the lead up to the 2018 UN High Level Meeting on Non-communicable Diseases, the resolution is a critical milestone in the journey to 2025.

Since world leaders came together for the UN High Level meeting (HLM) on Non-communicable Diseases (NCDs) in 2011, the political will to address cancer as part of the coordinated global response to NCDs has continued to build. The World Health Organization (WHO) Global Action Plan on NCDs (2013–2020), included cancer-specific actions and indicators covering the full cancer care continuum. More recently, in 2015, we saw the inclusion of a clear standalone target for NCDs within the health goal of the Sustainable Development Goals (SDGs).

Despite these advances in global policy, new WHO data shows cancer-related deaths have increased from 8.2 million in 2012 to 8.8 million in 2015 *(1)* with a disproportionate burden in low- and middle-income countries (LMICs).

These countries are urgently seeking best-practice guidance for implementation of phased, feasible and quality national cancer control programmes, with a focus on timely cancer diagnosis and early, and potentially curative, treatment. These same concerns were echoed by civil society in the World Cancer Declaration Progress Report *(2)* , launched at the 2016 World Cancer Leaders' Summit in Paris. This unique publication collated 113 country reports showcasing national cancer control successes and underlined the lack of progress in early detection, diagnosis, treatment and care, especially in LMICs, where access to essential cancer medicines, technologies and trained oncology healthcare workers are limited.

Adopted in May 2017, the World Health Assembly resolution on cancer *(3)* is a direct response to these challenges, providing a clear framework for a health systems response to cancer, establishing the core disciplines and services for a holistic, impactful and scalable response. Our hope is that the resolution will help refocus efforts between now and 2025, and more immediately in the lead up to the 2018 UN HLM on NCDs. Scheduled to take place in mid-2018, this global meeting will provide a critical opportunity for reviewing progress, sharing good practices and stimulating new action by Member States to drive progress towards the 2025 target to reduce premature deaths from cancer and other NCDs by 25%.

2017 cancer resolution: Not just another "paper tiger"

In May every year, Ministers of Health from all over the world come together in Geneva to discuss global health challenges and policy at the World Health Assembly (WHA), the decision-making body of the WHO. This year, for the first time since 2005, Member States discussed efforts to address cancer prevention and control, and considered a resolution outlining recommended actions for Member States and the WHO Secretariat across the cancer care continuum. In the 12 years since 2005, the global health landscape has evolved, and there have been key areas of progress in cancer prevention and control, including the development of national cancer control plans in a majority of countries *(4)*; improved focus on cancer surveillance; country uptake of vaccines for infection-related

Figure 1: **Infographic from UICC's social media campaign for the 2017 cancer resolution**

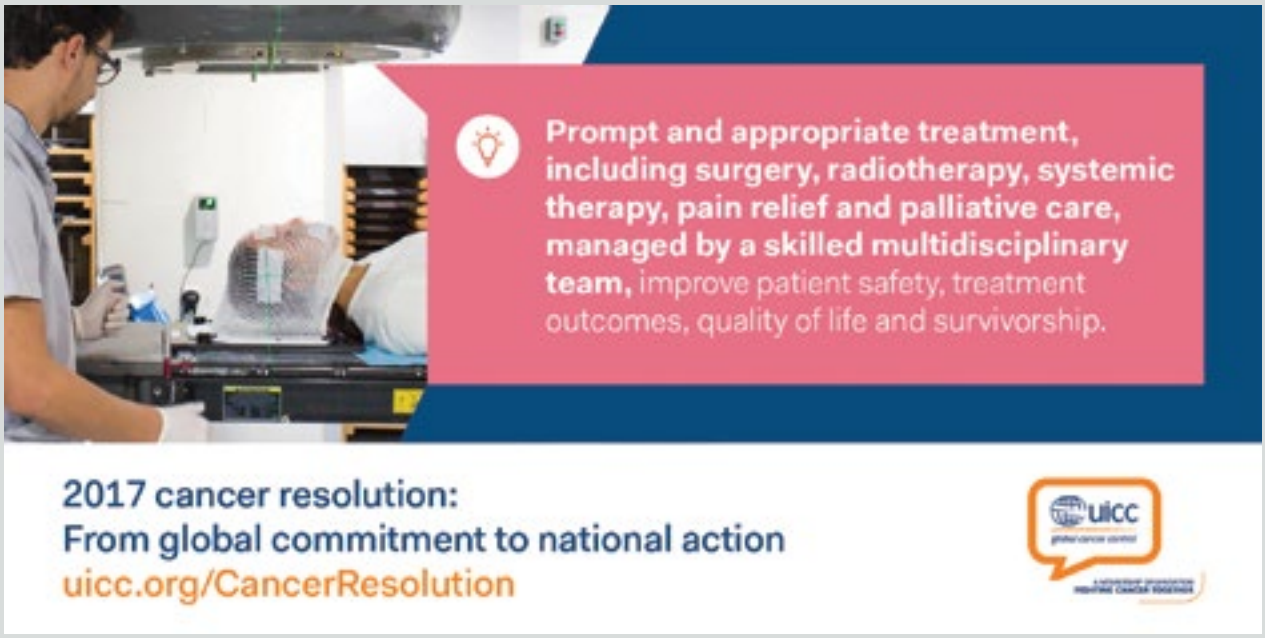


Figure 2: **Example of a supportive message from a key opinion leader for the 2017 cancer resolution**

cancers; early detection programmes; and an update to the WHO Model Essential Medicines List for cancer *(5)*. Following the 2011 and 2014 UN HLM on NCDs and the Global Action Plan on NCDs, there has been renewed focus on a health systems response for cancer as one of the lead NCDs.

Despite this, much of the effort so far to reduce mortality has focused on reducing incidence by addressing shared risk factors for cancer and other NCDs. Recognizing that this alone is insufficient in meeting global targets to reduce NCD mortality by 25% by 2025, and that many cancer deaths can be avoided if cases are diagnosed and treated early, the 2017 cancer resolution identifies four key drivers impacting cancer mortality by 2025 that are supported by the updated WHO cost-effectiveness recommendations for NCDs *(6)*, also approved at the 2017 WHA:

- Programmes for the early detection, accurate diagnosis and treatment of cervical, breast, colorectal and oral cancers.
- Development of partnerships, referral networks and centres of excellence for improving the quality of cancer diagnosis, treatment and care services and facilitating multidisciplinary cooperation.
- Training of health professionals at all levels of healthcare.
- Strengthening of palliative care and promotion of cancer survivors' follow-up and rehabilitation.

More specifically, the resolution underlines the importance of patient access to safe, effective and quality treatment and care that is affordable, and that would include effective surgery and anaesthesiology, pathology, radiotherapy and access to a limited number of essential cancer medicines, delivered by competent multidisciplinary teams. The resolution extends WHO's mandate to provide Member States with additional technical support in this regard. The WHO Secretariat is tasked with preparing a comprehensive technical report that examines pricing approaches and their impact on availability and affordability of medicines for the prevention and treatment of cancer, incentives for investment in research and development on cancer and innovation of these measures, and options that might enhance the affordability and accessibility of these medicines.

Speaking about the potential of the 2017 cancer resolution to have a real impact on patient outcomes, Dr Julie Torode, Deputy CEO, Union for International Cancer Control (UICC) said: "We are confident, and working hard, to ensure that it

will not be another 'paper tiger', disappeared from the global discourse. Rather, it will grow teeth through national action for impact in the lead up to 2025 and beyond."

Supporting the cancer resolution: A global effort to drive national action

During the sixty-ninth WHA held in May 2016, a side event on "Making the Right Investments for Cancer Control" (7), co-hosted by UICC, together with several Member States including Jordan, Malaysia, Honduras, Kuwait and Peru, culminated in a request to the WHO Executive Board for a cancer resolution to be placed on the agenda of the next WHA.

This call to action was reiterated at the November 2016 World Cancer Leaders' Summit in Paris, with UICC's CEO, Dr Cary Adams, encouraging the cancer community to "work together with their respective governments to ensure the development and adoption of a meaningful cancer resolution that would stimulate and support national action on the journey to 2025".

In January 2017, a first draft of the cancer resolution was presented to the WHO Executive Board for consideration; the response was very positive, with 28 Member States and 12 civil society organizations making statements affirming the importance of this resolution for catalysing national action, particularly in the areas of palliative care, childhood cancer, research needs and financing.

Following the Executive Board meeting, a core group of Member States led by Canada, and then Colombia, worked together intensively to integrate feedback and find consensus on language to navigate some of the more difficult topics, including availability and pricing of essential cancer medicines and use of HPV and HBV vaccination as a cost-effective strategy for the prevention of infection-related cancers. The final resolution text presented to the World Health Assembly for adoption on 30 May 2017 was co-sponsored by 18 Member States, with 44 Member States from across all regions and income settings vocalizing their support for the resolution during the ensuing discussions.

Alongside the WHA, UICC spearheaded a communications campaign to support cancer organizations and other key stakeholders to promote the cancer resolution, and showcase their commitment to using the resolution to stimulate action at the regional, national and local levels. The campaign has received wide early support on social media with over 1,000 tweets mentioning the #CancerResolution, and 40 key opinion leaders publishing supportive messages (Fig. 2).

Treatment for All: Building momentum to 2018

The 2018 UN HLM on NCDs will be the first formal opportunity since 2014 to review progress toward reaching the 2025 targets. It is a rare, critical moment for the cancer and wider NCD community to have a strong share of voice with Heads of State and other stakeholders who drive not just the health, but the 2030 development agenda, and who are key influencers in the allocation of resources to deliver cancer and NCD interventions, particularly in LMICs.

UICC calls for the cancer community to unite behind a clear and strong message to be delivered at the HLM, underlining the importance of increased human and financial resourcing for leaving no one behind in the countdown to 2025. While UICC recognizes the long-term impact of investing in cancer prevention, meeting the 2025 targets requires a health systems response for effective cancer management and improved patient outcomes. With this in mind, UICC will focus on delivering four priority pillars for action: (1) data for public health planning, monitoring and evaluation; (2) improved early detection for timely and accurate diagnosis; (3) early and quality treatment, including access to surgery, radiotherapy and medicines; and (4) management of advanced and metastatic disease through supportive and palliative care. ■

Rebecca Morton Doherty is Head of City Engagement & Impact for C/Can 2025: City Cancer Challenge, a new multi-sectoral UICC initiative to improve equitable access to cancer care in cities.

Box 1: C/Can 2025: City Cancer Challenge

"If a cancer resolution is going to make a difference by 2025, UICC must also play its part, and show leadership in the translation of global commitments into action. It is with this in mind that UICC is launching C/Can 2025, a multi-stakeholder initiative encouraging cities to take the lead on improving the health of their citizens and reducing inequities in access to quality cancer." UICC PRESIDENT PROFESSOR SANCHIA ARANDA, 2016 WORLD CANCER LEADERS' SUMMIT, PARIS, FRANCE

Today, more than 50% of the world's population live in urban environments. This figure is anticipated to grow to more than 60% by 2050. Cities, therefore, offer important opportunities to expand access to health services, including quality cancer care, for large numbers of the global population in a sustainable way.

Launched in January 2017, C/Can 2025 aims to increase the number of people with access to quality cancer treatment in cities around the world through a network of motivated partners including city leaders, governments, NGOs, UN agencies, and domestic and international businesses.

C/Can 2025 is already working with a small group of Key Learning Cities, including Cali, Asunción, Yangon, and Kumasi. Beginning in 2018, the ambition is to scale-up support to a wide network of cities that have a population greater than 1 million, in every region. To this end, on the occasion of the 2017 World Cancer Leaders' Summit held on 14 November in Mexico City, UICC launched a call to action inviting cities to join the initiative as C/Can 2025 Challenge Cities.

To learn more about the C/Can 2025: City Cancer Challenge visit: http://www.uicc.org/what-we-do/convening/ccan-2025-city-cancer-challenge

Since joining UICC in 2011, Rebecca has coordinated advocacy efforts with a focus on the global NCD agenda, and UICC's priority advocacy areas including cancer planning, and equitable access to cancer treatment and care. She has a BA in Political Sciences and an MSc in Development. Rebecca has spent over 10 years in the NGO sector, with a focus on strategic communications and policy development in the global health and development fields.

Micaela Neumann is an Advocacy Manager in the UICC Advocacy & Networks team, with previous work experience in community engagement, mobile health, vaccination and HIV/AIDS programmes. With a background in social sciences, Micaela has a focus on grassroots, civil society engagement across the cancer control landscape. She is leading the work translating global commitments of the cancer resolution into national action by working with UICC members as part of the new "Treatment for All" initiative. Micaela has a Masters in Anthropology and Sociology of Development, and a BA in Interpersonal Communication Studies.

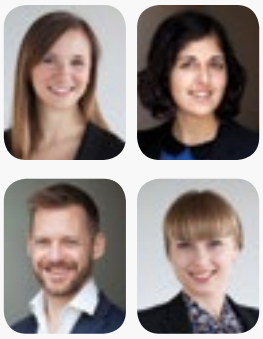
Dr Julie Torode is UICC's Deputy CEO and Advocacy & Networks Director. Since joining in 2008, she has led work on the TNM classification, the International Journal of Cancer, as well as UICC's capacity-building projects in childhood cancer, cervical cancer, access to pain relief, and education and training. Dr Torode has established key partnerships for UICC uniting efforts on the foundations of cancer control – the Global Initiative for Cancer Registration and the International Cancer Control Partnership. With a PhD in Chemistry, Julie entered the health and oncology arenas through leading clinical trials work, with a focus on breast and gynaecologic cancer.

References

1. http://www.who.int/cancer/en/
2. http://www.uicc.org/who-we-are/world-cancer-declaration
3. http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_ACONF9-en.pdf
4. 64% of countries with operational, funded cancer policies strategies or plans (IARC, 2014)
5. http://www.who.int/medicines/publications/essentialmedicines/en/
6. http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_27-en.pdf
7. http://www.uicc.org/are-we-making-right-investments-cancer-control-global-dialogue

INCREASING ACCESS TO CANCER CARE: HOW CAN WE GUIDE AND TRACK ACTIONS BY PHARMACEUTICAL COMPANIES?

BETH BOYER (TOP LEFT), RESEARCHER; **CLARKE COLE** (TOP RIGHT), RESEARCHER; **DANNY EDWARDS** (BOTTOM LEFT), RESEARCH PROGRAMME MANAGER AND **STINE TROLLE** (BOTTOM RIGHT), RESEARCHER, ACCESS TO MEDICINE INDEX, ACCESS TO MEDICINE FOUNDATION, THE NETHERLANDS



The Access to Medicine Index has been analyzing 20 of the largest R&D-based pharmaceutical companies by revenue on how they address access to medicines in LMICs for over ten years. Cancer has previously not been included within the disease scope of the Index. As the burden of cancer grows in low- and middle-income countries, the decision was made to include cancer in the 2018 index. The complexity of cancer, however, posed a number of challenges that needed to be addressed. By including cancer, the Index aims to incentivize companies to engage in strong, sustainable access programmes for cancer care, to support the appropriate strengthening of health systems to accommodate the latest treatments, and to find ways of facilitating access to the most effective medicines currently on the market.

Cancer incidence and mortality is on the rise in low- and middle-income countries (LMICs). Over half of all new cancer cases (57%) and cancer deaths (65%) in 2012 occurred in LMICs *(1)*. This is likely to increase due to population ageing and decreasing mortality from other causes. The challenges of providing cancer care in LMIC settings are compounded by poor disease surveillance and the relatively poor strength of local health systems.

While national governments shoulder the main responsibility for putting cancer care systems into place, pharmaceutical companies also have a unique role to play. There is a clear opportunity to motivate such companies – the developers and manufacturers of life-saving oncology products – to do more for cancer patients in LMICs.

At the Access to Medicine Foundation, our mission is to stimulate pharmaceutical companies to improve access to medicine for the people living in low- and middle-income countries. We identify ambitious but achievable actions that pharmaceutical companies can be expected to take in this regard – which we publish as a clear, consensus-based framework that pharmaceutical companies can use to organize their access-to-medicine activities.

The Foundation is an independent, non-profit organization funded by the UK Department for International Development, the Bill & Melinda Gates Foundation, the Dutch Ministry of Foreign Affairs, the Dutch Ministry of Health, and the Dutch National Postcode Lottery. Our in-house research team is responsible for the analysis of pharmaceutical companies and operates fully independent of our donors and the pharmaceutical industry.

Every two years, we measure how well pharma companies are meeting the expectations set out in our framework, publishing our findings in the Access to Medicine Index: a ranking of 20 of the world's largest research-based pharmaceutical companies (by revenue) on how they make medicine more accessible in LMICs.

By publicly recognizing the best performers, the Index spurs pharmaceutical companies to compete to be the best. The Index has now been published five times, starting in 2008. Each iteration has found evidence that companies are increasing their focus on access to medicine in LMICs.

Cancer has never before been included in the scope of the Index. However, given its growing importance on the access agenda, the decision has been made to include cancer in the next index. In this article, we explore the challenges this posed and how they have been addressed.

How the Index works

The Access to Medicine Index measures companies across seven areas of behaviour linked to access to medicine:

strategy, governance, R&D, pricing, licensing, capacity building and donations. It captures company behaviour in relation to defined sets of countries, diseases and products across indicators derived through multi-stakeholder consensus. Data for each metric is scored and then weighted before being aggregated into the final ranking of the Access to Medicine Index. During the review of the methodology for each Index, our research team consults with specialists from multilateral organizations, governments, research institutions, the pharma industry, NGOs, patient organizations and investors, among others.

Why address cancer now?

In 2015, a decision was made not to include cancer in the 2016 Access to Medicine Index. This was not straightforward: some stakeholders felt that the Index should continue to focus on the highest-burden or neglected diseases, while others expressed strong views that companies' access initiatives related to cancer needed to be mapped and encouraged. The role of R&D-based companies in access to cancer care was then unclear. This decision was provisional, to be reviewed before the 2018 Index.

The majority of deaths from cancer occur in LMICs; in Africa alone, cancer kills 50% more people per year than malaria *(1)*. In 2015 there was a significant increase in the number of cancer medicines included on World Health Organization's Model Essential Medicines List (WHO EML); three more were added during the 2017 update *(2)*. Research and development (R&D) activity for cancer treatment has expanded rapidly, and the global oncology market is expected to grow from around US$ 105 billion to US$ 150 billion by 2020 *(3)*. As countries implement national cancer control plans it becomes increasingly important for pharmaceutical companies to play a role in ensuring access to key products for cancer and to contribute to the development of resilient health systems.

With these factors in mind, the Foundation analyzed available data from companies about their current access to cancer activities. In May 2017, the Foundation published the first analysis of company engagement in access to cancer care. This study found that 16 of the 20 companies in the Access to Medicine Index are taking action to improve access to cancer care in LMICs *(4)*. The results of this study demonstrate clear company engagement and an opportunity to support actions and efforts. The clear evidence of company activity, in tandem with the reasons outlined above, made a strong case for the inclusion of cancer in the 2018 Access to Medicine Index.

Challenges of including cancer in the Index

An overarching concern with cancer care is how to account for the varying strength of national healthcare systems. For example, China, India, and Brazil have relatively strong health systems, which are better equipped for the management of cancer, while countries such as Kenya and South Africa do not yet meet the basic infrastructure requirements for cancer treatment *(5)*. Many LMICs also place low prioritization on cancer. Many countries do not yet have, or are in the process of implementing a cancer control strategy or plan *(6)*.

Companies may be less likely to want to engage in countries with low government prioritization or support, or in countries with less existing donor and NGO presence. They may show preference for countries with better capacity for introducing cancer products. Conversely, some companies may also see a long-term benefit from engaging in weaker health systems, thereby building and securing future markets for their medicines. For example, although Kenya currently does not meet infrastructure standards for cancer treatment, it receives more attention from company capacity building initiatives than other countries in scope *(4)*, likely due to government prioritization, an active network of partners, and continued capacity improvement over recent years. The 2018 Index will need to acknowledge this context and how companies' initiatives reflect the state of national health systems.

While taking this country variation into consideration, the research team of the Foundation considered two critical issues when developing its framework of metrics. First, which cancers should companies be focusing on? Second, how should companies be strengthening health systems for managing cancer?

Bringing cancer into scope: by disease burden, the existence of key products or by the need for R&D?

Let's start with the first issue: which cancers should companies be focusing on, and hence be included in the Index? To date, the Access to Medicine Index has largely based its disease scope on global disease burdens (calculated in terms of Disability Adjusted Life Years, or DALYs). The main exceptions to this rule are the Neglected Tropical Diseases, where WHO prioritization is the defining criterion. If a disease is in scope, then the Index will examine how companies are addressing access to medicine for this disease, either through R&D, or by addressing the availability and affordability of existing products.

However, our team soon established that a unique approach would be needed for cancer – as "cancer" refers to a range of diseases with varying treatment options and disease burdens. Some cancers with the highest incidence globally (e.g., liver *(1)*) have few effective pharmaceutical treatment options, whereas other cancers with lower global incidence (e.g., Kaposi sarcoma) have several. The experts we talked to advised separate approaches for including cancers in the disease scope: one product-based approach to identify cancers with

effective products on the market where access is an issue; and one incidence-based approach for cancers where further R&D should be incentivized.

Which low-incidence cancers have clinically effective products on the market?

In 2014, the World Health Organization invited the Union for International Cancer Control (UICC) to review the existing paediatric and adult WHO EML. This was the first full review of cancer medicines for this list since 1999. Choices for inclusion were made using a combination of incidence data and potential impact of treatment. This brought the total number of cancer medicines on the WHO EML to 46 in 2015. In 2017, three more cancer medicines were added to the WHO EML, bringing the current total to 49. The Foundation team has used this recently updated WHO EML to bring cancers with high-impact available products into scope.

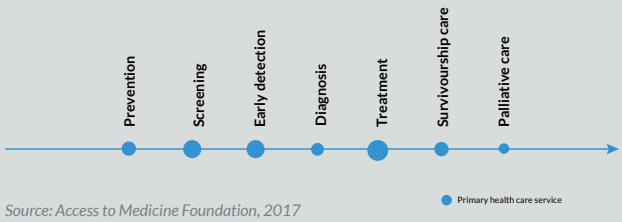
However, even products defined as "essential" by WHO often require well-equipped healthcare systems in order to be used effectively. For some products to be prescribed, patients must undergo genetic testing. For other products, particularly chemotherapy drugs, they are most effectively used in combination with one another. We will need to consider the varied strength of health systems when making specific recommendations on companies' approaches for registration and affordability.

Which cancers need further R&D for LMIC settings?

Oncology is one of the main focus areas for R&D by pharmaceutical companies. Pipelines are big: we have observed 22 FDA approvals for cancer products from companies in the Index since 2015, compared to only two for cardiovascular diseases *(7)*. The substantial focus in this area of R&D likely reflects the large commercial market potential for cancer treatments in high-income countries (HICs). While this serves as a strong incentive to drive innovation, it does not guarantee that successful products will be suitable for the needs and health system capacities of LMICs. This is particularly likely where new cancer treatments are targeted therapies and immunotherapies. Such products introduce new complexities into health systems, which may not be equipped to deal with them.

The Index aims to stimulate companies to address the needs of LMICs in their R&D projects. To do this, we need to bring cancers where LMICs have a clear R&D need into scope. Yet this R&D wish-list does not yet exist. To take a first step into this gap, we have developed an approach for selecting those cancers which impact LMICs to the greatest degree. One of our aims in publishing this list is to encourage companies to invest in oncology R&D specifically for LMICs.

Figure 1: Effective cancer management requires a sequence of health services, referred to as "the cancer continuum of care."*(4)*



Source: Access to Medicine Foundation, 2017

Our prioritization focuses on cancers with the highest global incidence rates. When it comes to incidence rates, stakeholders such as the UICC consider global data more appropriate than data from individual LMICs, which is typically weaker due to poor disease surveillance. Plus, country-level incidence data may be masked by communicable diseases. We have also included cancers with high incidence rates in countries in scope (despite the poor data) where these cancers are linked to infections that impose disproportionately high disease burdens on LMICs.

We have spoken with experts to explore whether certain types of R&D projects (such as immunotherapies or highly personalized treatments) should be considered irrelevant to the needs of populations in LMICs due to the complexity of deploying these therapies. Some argued that there is no clearly defined category of R&D projects that could be reasonably excluded from analysis in all countries within the Index scope. Furthermore, excluding such projects would risk potentially disincentivizing companies from also targeting LMIC needs when carrying out these types of R&D. As such, the pragmatic approach is to include all projects in our criteria for including cancers in this aspect of the disease scope.

Evaluating company engagement in capacity building for cancer care

Let 's turn our attention to the second issue: how to evaluate company engagement in capacity building for cancer care. When thinking about the disease scope, the comparative strength of national health systems has been a recurring theme. In the WHO's Global Status Report on NCDs in 2010, survey results showed "poor availability of basic technologies and treatment, particularly for cancer and diabetes in primary care, in many low-income and lower-middle-income countries *(8)*." Management of NCDs has typically been less prioritized by governments, leaving gaps in the strength of health systems to effectively manage them. Health systems must be able to provide access to not just medicines, but also to comprehensive care.

This can be particularly complicated for NCDs due to the wide range of infrastructure, medical devices, and skilled staff required. For cancer, health systems need to provide a

Table 1: **The process for the 2018 Access to Medicine Index Methodology Review**

2018 Access to Medicine Index Methodology Time Table	
Methodology Proposal Review by ERC #1	13 June 2017
Respond to ERC methodology feedback (any methodological changes)	June/July 2017
Methodology Proposal Review by ERC #2	18 July 2017
Final Methodology Report Published	October 2017

sequence of health services, often referred to as "the cancer continuum of care" (Fig. 1). Even the treatment step is more complex than dispensing medicines. Biologics, for example, must be kept cold and administered intravenously in specialty treatment centres to manage any adverse events *(5)*.

The need to strengthen health systems for managing cancer is very clear. While this is primarily the role of governments, pharmaceutical companies are well-positioned to take on an important supporting role in building capacity for comprehensive cancer care. There are opportunities for initiatives all along the continuum of care, from training healthcare professionals to investing in infrastructure. Indeed, our May 2017 study Improving Access to Cancer Care found that 50% (71 out of 129) of companies' access initiatives relating to cancer involve capacity building *(4)*. Companies are aware of their potential role in capacity building for cancer and are taking action. The questions the 2018 Index faces are: how to identify high-quality initiatives and how to encourage companies to adopt successful models.

In consultation with stakeholders, we have developed a set of criteria to be used for the qualitative evaluation of capacity building initiatives. This includes investigating whether among other factors initiatives are carried out in partnership, aim for sustainability and, particularly relevant in the case of cancer, how company initiatives address the needs of and strengthen the capacity of the local healthcare system. The 2018 Index will place a greater emphasis on health system strengthening initiatives in part because of their importance in supporting cancer care.

Conclusion and next steps

The Expert Review Committee (ERC) of the Access to Medicine Index considered again whether or not to include cancer in the 2018 Access to Medicine Index on 13 June 2017. Taking into account the challenges identified by this article, the ERC recommended yes, it should be included. The timing of this decision coincides well with the increasing attention and prioritization of cancer by the global health community, exemplified by the adoption of a resolution on cancer prevention and control by the WHO in May this year *(9)*.

Pharmaceutical companies have a clear, supportive role to play and are already active. The inclusion of cancer will provide us with new opportunities to encourage companies to do more and to show them how their peers are harnessing their strengths in product development, deployment and health system strengthening.

The approaches laid out here reflect the methodology for the inclusion of cancer in the 2018 Index, as presented in our Methodology Report published in October of this year. Our goal is to incentivize companies to engage in strong, sustainable access programmes for cancer care, to support the appropriate strengthening of health systems to accommodate the latest treatments, and to find ways of facilitating access to the most effective medicines currently on the market. The inclusion of cancer in the 2018 Index is an important step towards this goal. The 2018 Access to Medicine Index will be published in November 2018. ■

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References

1. Ferlay J; Soerjomataram I; Ervik M; Dikshit R; Eser S; Mathers C; Rebelo M; Parkin DM; Forman DBF. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide [Internet]. IARC Cancer Base No. 11. Lyon, France; 2013. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
2. WHO | WHO updates Essential Medicines List with new advice on use of antibiotics, and adds medicines for hepatitis C, HIV, tuberculosis and cancer [Internet]. WHO. World Health Organization; 2017 [cited 2017 Jun 8]. Available from: http://www.who.int/mediacentre/news/releases/2017/essential-medicines-list/en/
3. IMS Health. Global Market for Cancer Treatments Grows to $107 Billion in 2015, Fueled by Record Level of Innovation [Internet]. 2016 [cited 2002 Jul 20]. Available from: http://www.imshealth.com/en/ about-us/news/ims-health-study-global-market- for-cancer-treatments-grows-to-107-billion-in- 2015
4. Oomen, Karin PQ; Karuranga, Suvi; Iyer JK. Improving Access to Cancer Care: A first analysis of pharmaceutical company actions in low and middle income countries. Amsterdam; 2017.
5. QuintilesI MS Institute. Ensuring Essential Medicines Satisfy Priority Healthcare Needs of Populations. Parsippany, NJ; 2016.
6. National Plans | ICCP Portal [Internet]. [cited 2017 May 8]. Available from: http://www.iccp-portal.org/map
7. CenterWatch [Internet]. [cited 2017 May 15]. Available from: https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/12/oncology
8. World Health Organization. Tackling NCDs : the capacity of countries to respond. In: Global Status Report on Non-Communicable Diseases. Geneva: WHO; 2010. p. 72–83.
9. WHO. Seventieth World Health Assembly: Cancer prevention and control in the context of an integrated approach [Internet]. WHO. 2017 [cited 2017 Jun 1]. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_ACONF9-en.pdf

THE IMPORTANCE OF GLOBAL SURVEILLANCE OF CANCER SURVIVAL FOR CANCER CONTROL: THE CONCORD PROGRAMME

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CONCORD is a prize-winning[i] programme for the global surveillance of cancer survival. It started in 1999, with the aim of monitoring population-based cancer survival trends worldwide. The CONCORD Working Group now includes over 500 collaborators.

Why population-based survival?

Population-based survival is a key measure of the overall effectiveness of the health system in managing cancer in a given country or region.

Randomized trials tell us if a new treatment is better than the current standard treatment, but patients recruited to trials are not representative of all cancer patients: they are usually selected on age, stage of disease and lack of comorbidity and they are treated with close adherence to protocol in specialized cancer units by the most research-active physicians. Typically, also, fewer than 5% of adult cancer patients are treated in clinical trials *(1)*, although for children in developed countries, the proportion may be 70% or more.

By contrast, population-based cancer survival reflects the overall effectiveness of the health system in dealing with cancer *(2)*. It is a measure of the average survival achieved by *all cancer patients*, young and old, rich and poor, with and without comorbidity, and with early or advanced disease at diagnosis.

Population-based survival is estimated from data provided by population-based cancer registries, which routinely collect, on a continuous basis, a basic data set on every person diagnosed with cancer in a defined population, typically residents of a country, or a defined geographical area such as a province or state. The basic data set covers the patient's date of birth, sex and place of residence; the topography, morphology and behaviour of the tumour; the basis of diagnosis and the date of diagnosis. Most long-standing cancer registries also collect information on each patient's last known vital status (alive, dead, emigrated) and the date of the last known vital status. This information on the follow-up of cancer patients is crucial to estimate survival.

Follow-up can be determined actively (*active follow-up*), by direct contact with the patient, their family or their GP, or passively (*passive follow-up*), by performing a record linkage between the cancer registry database and a national database of all deaths, such as the National Death Index (NDI) in the United States. With active follow-up, it is possible to determine exactly the date of the last known vital status for patients who are dead and those who are alive. With passive follow-up, the date of death of patients who have died is exactly determined when a record in the cancer registry is successfully linked to a death record for the same person in the national death index. Patients whose cancer registration record could not be matched to the national death index during record linkage are presumed to be alive at the date on which the linkage was performed *(3, 4)*. Passive follow-up is widely used because it is cheaper than active follow-up and it is known to be efficient if the infrastructure is adequate *(3)*.

Cancer survival and the stage of disease at diagnosis

The stage of disease at diagnosis is a key determinant of long-term survival for almost all malignancies. Differences in population-based cancer survival between population sub-groups (e.g., rich and poor *(5)*, black and white *(6)*, Maori and non-Maori *(7)*) within a country, or differences between countries *(8)*, may be explained, at least in part, by differences in the stage of disease at diagnosis in the cancer patient populations being compared. The survival for all women

[i] *https://betterhealthforall.org/2016/05/16/fph-global-public-health-award-global-surveillance-of-population-based-cancer-survival/*

with breast cancer, for example, may be lower in one country than another because women in that country are generally diagnosed with more advanced disease that is less susceptible to treatment of curative intent. Alternatively, their survival may be poorer at each stage of disease, which may imply that optimal treatment is not available in that country, particularly for early-stage tumours: survival for very advanced tumours is similar in most countries. More advanced disease and lower stage-specific survival may both play a role in international differences in survival.

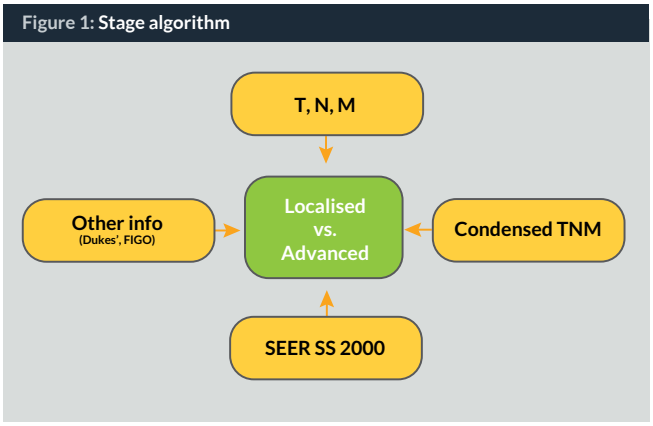
During the past two decades, most cancer registries have begun collecting information on the stage of disease at diagnosis, and whether the patient received surgery, radiotherapy, chemotherapy, hormonal or other systemic therapy, and if so, the date of first treatment. However, the proportion of registrations with incomplete data on stage and treatment is still very high, even in some developed countries.

The Tumour Nodes and Metastasis (TNM) classification has been recognized as the gold standard for the collection of data on stage of disease for many years *(9, 10)*, but it is still not sufficiently widely used. Several other stage classifications are still used in many countries. Surveillance, Epidemiology and End Results Summary Stage 2000 (SEER SS 2000) *(11)* is used in the United States, Australia and Israel, and a simplified form of TNM (condensed TNM) is used in many European countries *(12)*. Several cancer-specific stage classifications are also widely used, such as Dukes' stage for colorectal cancer *(13, 14)*, FIGO stage for cancers of the ovary and cervix *(15)*, and Ann Arbor stage for lymphomas *(16)*. Furthermore, some cancer registries still use local classifications. Data on stage in some of these classifications can be converted into equivalent categories in the TNM classification, but the conversions can be complex and time-consuming, especially when the cancer data being analysed cover long periods of time, during which both TNM and the parent classification may have undergone revision.

Long-term trends in stage-specific survival may also be affected by coding conversion issues. In recent analyses of survival trends by race and stage at diagnosis in the United States, patients were grouped by year of diagnosis into two calendar periods (2001–2003 and 2004–2009) to reflect changes in the methods used by United States registries to collect data on stage at diagnosis *(17)*. From 2001, most registries coded stage directly from the source data to SEER SS 2000 *(11)*. From 2004, all registries began to derive Summary Stage 2000 from 15 pathological and clinical data items, using the Collaborative Staging System *(18)*.

To address these problems in international comparisons of cancer survival, the CONCORD Central Analytic Team has developed a complex algorithm that is designed to harmonize as far as possible all the available data on stage at diagnosis. This is based on our previous work in the EUROCARE and CONCORD high-resolution studies *(19–22)*. The algorithm summarizes all the data on stage into two broad categories, localized and advanced. It gives priority to TNM stage (pathological and clinical), then compensates for any missing information on TNM stage with the size of the tumour and/or the number of positive lymph nodes, then with SEER SS 2000, or condensed TNM, or FIGO or Dukes' stage, depending on the tumour (Figure 1 shows a simplified version of the CONCORD stage algorithm).

Figure 1: Stage algorithm



This algorithm enables much wider international comparison of cancer survival by stage than would otherwise be possible. In an ongoing study of breast cancer survival by stage at diagnosis, for example, restriction of the analyses to data sets in which at least 70% of tumours had been staged to the TNM classification would have limited the comparison to 34 cancer registries and 19 countries. After deployment of the algorithm to assign localized or advanced stage by integrating all the available data from each registry, it was possible to include data sets with at least 70% of staged tumours from 109 registries and 39 countries.

For international comparisons of cancer survival by stage on a worldwide scale, our main goal is to be able to categorize stage as localized and advanced. This simple dichotomy is helpful for comparisons of stage distributions between populations, as well as for stage-specific survival comparisons. It offers an opportunity to compare the distribution of stage at diagnosis in both developed and developing countries using a categorization which is likely to be more robust than if we pretended that stage could be precisely assessed for all cancer patients in every population we are comparing.

However, a much wider international implementation of the TNM stage classification would be most desirable.

The CONCORD programme

The first CONCORD study *(23)* produced five-year survival estimates for 2 million patients diagnosed with breast,

colorectal or prostate cancer during 1990–1994 and followed up to 1999. The data were provided by 101 cancer registries in 31 countries, 16 of which with national coverage. Global variation in survival was very wide: generally higher in North America, Australia and Japan, and in northern, western, and southern Europe, and lower in Algeria, Brazil and countries in eastern Europe.

In 2015, the second cycle of the programme (CONCORD–2) established long-term surveillance of cancer survival worldwide, for the first time *(24)*. CONCORD-2 provided cancer survival trends for 25,676,887 patients diagnosed during the 15-year period 1995–2009 with one of 10 common cancers (stomach, colon, rectum, liver, lung, breast (women), cervix, ovary and prostate, and leukaemia) that collectively represented 63% of the global cancer burden in 2009. The data were provided by 279 population-based cancer registries that covered a total population of 896 million people in 67 countries. In 40 of those countries, the data provided 100% coverage of the national population.

Worldwide differences in survival were striking. Age-standardized five-year net survival from colon, rectal and breast cancers had increased steadily in most developed countries up to 2009, reaching 60% or more in 22 countries for colon and rectal cancers, and up to 85% or more in 17 countries for breast cancer in women. For cancers of the liver and lung, however, 5-year survival was still below 20% everywhere. Striking rises in prostate cancer survival were seen in many countries, but survival still varied from less than 60% in Bulgaria and Thailand to 95% or more in Brazil, Puerto Rico and the United States. Survival from cervical cancer also ranged widely, from below 50% to over 70%, and improvements over the 15 years to 2009 were generally small. For women with ovarian cancer, 5-year survival was above 40% in only 20 of the 67 countries. For stomach cancer, 5-year survival was very high in Japan and South Korea (54–58%), but less than 40% in all other countries. Five-year survival from adult leukaemia in Japan and South Korea (18–23%) was lower than in most other countries. This striking contrast may be attributable to differences in the distribution of the main types of leukaemia between Asian and Caucasian populations: survival from chronic lymphocytic leukaemia is generally very high, but it is comparatively uncommon in Asian populations. More detailed analyses of leukaemia survival are in progress.

For acute lymphoblastic leukaemia in children, survival was less than 60% in several countries, but close to 90% in Canada, the United States and four European countries, suggesting major deficiencies in many countries in the management of what is now considered a largely curable disease *(25)*.

CONCORD–2 was covered by TV, radio, press and wire services worldwide. The Altmetric score of 800, reflecting social media impact, is higher than 99.98% of 6.5 million articles evaluated to date. Results have been incorporated into the American Cancer Society's *Cancer Atlas (26)*. The article has been cited over 750 times since 2015 (Google Scholar).

Impact on cancer control strategies

With publication of the CONCORD–2 study, health ministers in 67 countries – home to two-thirds (4.8 billion) of the world's population – finally obtained cancer survival estimates that are methodologically rigorous and internationally comparable, to help them prioritize and formulate cancer control strategies *(27)*. For some countries, this was the first time such data had been available.

The US National Cancer Institute recognized the impact of CONCORD–2 in an invited commentary for *The Lancet*, noting that global analyses of cancer survival provide an opportunity for lessons from countries with successful cancer control initiatives to be applied to other regions. They added that the availability of better data "provides a clearer picture of the effect of cancer control programmes on the ultimate goal of improving survival and reducing the effect of cancer on the social and economic development of countries" *(27)*.

The US Centers for Disease Control (CDC) described CONCORD–2 as the start of global surveillance of cancer survival[ii], with survival estimates "that can be compared, so scientists can begin to determine why survival differs among countries. This could lead to improvements in cancer control programmes".

CONCORD–2 results underpinned new cancer strategy in England in July 2015 *(28, 29)*.

In September 2015, the International Atomic Energy Agency's Programme for Action on Cancer Therapy (PACT) used CONCORD–2 results to launch an ambitious worldwide campaign to highlight the global divide in survival and to raise awareness of persistent inequalities in access to life-saving cancer services *(30)*.

CONCORD–3

The third cycle of the CONCORD programme updates worldwide surveillance of cancer survival trends to include patients diagnosed during 2010–2014, with follow-up to 31 December 2014. It includes 15 malignancies that represent 75% of the global cancer burden: oesophagus, stomach, colon, rectum, liver, pancreas, lung, melanoma of the skin, breast (women), cervix, ovary and prostate in adults (15–99 years), and brain tumours, lymphomas and leukaemias in both adults and children (0–14 years) *(33)*. We have examined geographic variation and time trends in cancer survival for 70

[ii] *https://www.cdc.gov/cancer/dcpc/research/articles/CONCORD-2.htm*

or more countries. Where adequate data are available, we will examine survival by stage at diagnosis, morphology and race/ethnicity. We will also include information on the first course of treatment for each patient.

The results of CONCORD–3 can be expected to have a substantial impact on the public, in the media and in the scientific and public health community.

CONCORD and OECD

From 2017, the Organisation for Economic Co-operation and Development (OECD) will include survival estimates from the CONCORD programme for 48 countries in its biennial publication series *Health at a Glance (31)*, and regional online versions for Asia, Europe and Latin America. This represents formal recognition by an international agency of the global coverage, methodological rigour and international comparability of the CONCORD survival estimates, which will become crucial for the evaluation of health systems performance in all OECD Member States. Survival estimates from the CONCORD programme will therefore become the *de facto* standard for international cancer survival comparisons. The results will also help monitor progress toward the overarching goal of the 2013 World Cancer Declaration *(32)*, to achieve major improvements in cancer survival by 2020. ■

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References

1. Nass SJ, Moses HL, Mendelsohn J, editors. A national cancer clinical trials system for the 21st century: reinvigorating the NCI Cooperative Group Program. Washington, DC: Institute of Medicine; 2010
2. Coleman MP. Cancer survival: global surveillance will stimulate health policy and improve equity. *Lancet* 2014; 383: 564-73
3. Johnson CJ, Weir HK, Fink AK, et al. The impact of National Death Index linkages on population-based cancer survival rates in the United States. *Cancer Epidemiol* 2013; 37: 20-8
4. Johnson CJ, Weir HK, Yin D, Niu X. The impact of patient follow-up on population-based survival rates. *J Registry Manage* 2010; 37: 86-103
5. Rachet B, Woods LM, Mitry E, et al. Cancer survival in England and Wales at the end of the 20th century. *Br J Cancer* 2008; 99 (Suppl. 1): 2-10
6. Kish JK, Yu M, Percy-Laurry A, Altekruse SF. Racial and Ethnic Disparities in Cancer Survival by Neighborhood Socioeconomic Status in Surveillance, Epidemiology, and End Results (SEER) Registries. *JNCI Monographs* 2014; 2014: 236-43
7. Sandiford P, Abdel-Rahman ME, Allemani C, Coleman MP, Gala G. How many cancer deaths could New Zealand avoid if five-year relative survival ratios were the same as in Australia? *Aust N Z J Public Health* 2015; 39: 157-61
8. Coleman MP, Forman D, Bryant H, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. *Lancet* 2011; 377: 127-38
9. Sobin LH, Wittekind C, editors. *TNM Classification of Malignant Tumours*. New York: John Wiley & Sons; 1997
10. Hermanek P, Sobin LH. *TNM Classification of Malignant Tumours*. Geneva: UICC; 1992
11. Young JL, Roffers SD, Ries LAG, Fritz AG, Hurlbut AA. *SEER Summary Staging Manual - 2000: Codes and Coding Instructions*. NIH Pub. No. 01-4969. Bethesda, MD: National Cancer Institute; 2001
12. Berrino F, Brown C, Moller T, Sobin LH, Faivre J. ENCR recommendations: condensed TNM for coding the extent of disease. Lyon: European Network of Cancer Registries, 2002
13. Dukes CE. The classification of cancer of the rectum. *J Pathol Bacteriol* 1932; 35: 323-32
14. Astler VB, Coller FA. The prognostic significance of direct extension of carcinoma of the colon and rectum. Ann Surg 1954; 139: 846-52
15. Benedet JL, Bender H, Jones H, Ngan HY, Pecorelli S. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. *Int J Gynaecol Obstet* 2000; 70: 209-62
16. Armitage JO. Staging non-Hodgkin lymphoma. *CA Cancer J Clin* 2005; 55: 368-76
17. Allemani C, Harewood R, Johnson C, et al. Population-based cancer survival in the US: data, quality control and statistical methods [in press]. *Cancer* 2017: xx-yy
18. Cronin KA, Ries LAG, Edwards BK. Preface [Collaborative staging and its impact on cancer registry data: information for data users on analysis and interpretation of registry data]. *Cancer* 2014; 120: 3755-7
19. Allemani C, Sant M, Weir HK, et al. Breast cancer survival in the US and Europe: a CONCORD high-resolution study. *Int J Cancer* 2013; 132: 1170-81
20. Allemani C, Rachet B, Weir HK, et al. Colorectal cancer survival in the USA and Europe: a CONCORD high-resolution study. *BMJ Open* 2013; 3: e003055
21. Allemani C, Storm H, Voogd AC, et al. Variation in 'standard care' for breast cancer across Europe: a EUROCARE-3 high resolution study. *Eur J Cancer* 2010; 46: 1528-36
22. Minicozzi P, Kaleci S, Maffei S, et al. Disease presentation, treatment and survival for Italian colorectal cancer patients: a EUROCARE high resolution study. *Eur J Public Health* 2013
23. Coleman MP, Quaresma M, Berrino F, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008; 9: 730-56
24. Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet* 2015; 385: 977–1010
25. Pui CH, Evans WE. A 50-year journey to cure childhood acute lymphoblastic leukemia. *Semin Hematol* 2013; 50: 185-96
26. Aggarwal A, Allemani C, Armstrong B, et al. The Cancer Atlas. 1 August 2015 2015. http://canceratlas.cancer.org/ (accessed 2 August 2015
27. Harlan LC, Warren JL. Global survival patterns: potential for cancer control. *Lancet* 2015; 385: 926-8
28. Walters S, Benitez-Majano S, Muller P, et al. Is England closing the international gap in cancer survival? *Br J Cancer* 2015; 113: 848-60
29. Independent Cancer Taskforce. Achieving world-class cancer outcomes: a strategy for England 2015-2020. London: NHS England, 2015
30. International Atomic Energy Agency. PACT's new campaign raises awareness of the persistent inequalities in access to lifesaving cancer services: PACT highlights the growing global divide in cancer survival rates. Vienna: IAEA; 2015
31. Organisation for Economic Co-operation and Development. *Health at a Glance* 2017: OECD indicators. Paris, France: OECD Publishing; 2017.
32. Union for International Cancer Control. World Cancer Declaration 2013. 2013. http://www.uicc.org/world-cancer-declaration (accessed 11 March 2015
33. Allemani C, Matsuda T, Di Carlo V, et al. and the CONCORD Working Group. Global surveillance of trends in cancer survival: analysis of individual records for 37,513,025 patients diagnosed with one of 18 cancers during 2000-2014 from 322 population-based registries in 71 countries (CONCORD-3). *Lancet* 2017, in press

CERVICAL CANCER

TACKLING THE BURDEN OF CERVICAL CANCER: LESSONS FROM MALAWI AND OTHER LOW- AND MIDDLE-INCOME COUNTRIES

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In poor countries cervical cancer typically presents late, with high associated mortality. This article focuses on Malawi, but the issues are relevant to other low-income settings. HPV testing and HPV vaccination offer the prospect of significant reductions in cervical screening mortality. If this is to be achieved there is a need for governments to accept HPV testing and vaccination and to make them a central component of health policy and to address educational and training needs amongst health workers and the wider population.

The burden of cervical cancer in LMICs

Cervical cancer poses a significant global burden, particularly in the low- and middle-income countries (LMICs); it is the fourth most common female cancer, with approximately 528,000 cancers in 2012 *(1, 2)*. In LMICs it accounts for almost 12% of female cancers – most (about 85%) of the global burden is in these countries. About 87% of deaths from cervical cancer also occur in poor regions of the world *(1)*; women who suffer poverty, or are socially disenfranchised are far more likely to develop, and die from, cervical cancer – such women are likely to present much later, and to have limited access to diagnostic and treatment services *(3)*. Yet cervical cancer is largely preventable – see Table 1 for a summary of prevention approaches. Public health interventions, such as HPV vaccination for girls aged 9–13 years, and screening with treatment of precancerous lesions could bring incidence and mortality rates down to those seen in western countries *(4, 5)*; indeed, the WHO considers these interventions to be "best buys", as articulated in their Global Action Plan for the Prevention and Control of Non-communicable Diseases (2013–20).

Cervical cancer in Malawi

Malawi was recently reported to have the highest rate of cervical cancer in the world with a world age-standardized rate of 75.9 per 100,000 *(3)*. In common with many other countries, the Malawian Ministry of Health Strategic Plan includes provision of cervical screening using Visual Inspection with Acetic Acid (VIA) but delivery is challenging and treatment of early lesions is often unavailable *(6, 7)*. Our studies of a screening population in Nkhoma in rural Malawi suggest a prevalence of around 20% across the age range but more than double this in HIV+ women *(8)*.

Risk factors for cervical cancer

Overwhelmingly, cervical cancer risk is determined by the presence of HPV infection *(9)*; three important risk factors include the number of lifetime sexual partners *(10)*, HIV infection and co-infection with other sexually-transmitted diseases such as Chlamydia trachomatis and Herpes Simplex *(11, 12)*. Additional risk factors for cervical cancer include a history of smoking, younger age at first intercourse and at first pregnancy, high parity, and long-term use of oral contraceptives *(9)*. High rates of HIV infection (which promotes the progression of precancerous lesions) in areas such as sub-Saharan Africa have also contributed to higher cervical cancer incidence *(13)*.

Cervical cancer – its link to HPV infection

Evidence has gradually accumulated over the last several decades, on the link between HPV infection and cervical cancer *(14)*. Natural history and follow up studies have clearly shown that infection with high risk (HR) HPV precedes the development of cervical cancer by several years, that sexual transmission is the predominant mode of HPV acquisition and that HPV 16 is

a more potent carcinogen than nicotine *(14, 15)*; over 170 types of HPV are formally recognized *(16)*, and we now have a detailed understanding of HPV biology and pathogenesis *(17)*.

Infection with HR-HPV is very common, with around 80% of men and women expected to have an HPV infection during their life-time. Most regress without clinical symptoms. Indeed, HPV often coexists with its host over long periods in a kind of immune tolerance. Persistence of infection and progression to cancer may therefore be linked to a failure of the immune response, although no obvious link to HLA type or other susceptibility indicators has been made. In immunosuppressed people, whether due to infection such as HIV or induced through organ transplantation, HPV is more common than in HIV negative populations, with a broader range of types and more multiple infections *(18)*. HPV prevalence varies greatly from country to country, ranging from an average of 6.6% in Europe to 22.9% in Africa *(19)*. However, breakdown by age shows much wider variation, with an inverse relationship between age and prevalence in many countries but high across all ages in some poor countries *(20)*.

Finding the best approach to cervical screening in LMICs

Much of the evidence of the benefits of cervical screening programmes comes from affluent areas of the world where screening is long-established, such the Nordic countries *(21)* and the United Kingdom *(22, 23)*. Cervical cancer has become a rare disease in high-income countries, and there is widespread consensus that these very substantial benefits would not have come about in the absence of substantial investments in screening *(24)*. For decades, cervical screening in many high-income countries has been reliant on Papanicolaou (Pap) screening by conventional or liquid-based cytology, although HPV triage and even primary, testing is increasingly being adopted in a number of countries, and indeed recommended *(25, 26)*. Screening is usually population-based and organized (compared to opportunistic), and comprehensive quality assurance guidance is available *(27)*. Organized screening programmes seek to ensure that the steps of call and recall within a defined target population, investigation, treatment and follow-up (including access to palliative care) are in place, i.e. that screening is understood as a process, not merely as the test.

Such cervical screening programmes are out of reach of most LMICs. The World Health Organization (WHO) has issued guidance with recommendations for countries with differing resources – in addition to vaccination of girls before the initiation of sexual activity, screening of women aged 30–49 years is recommended *(26)*. Screening may involve HPV testing, cytology or visual inspection with acetic acid (VIA), with the screening approach used in any particular context (country, or healthcare facility) dependent on factors that include the balance of benefits and harms, the potential for women to be lost to follow-up, cost and availability of the necessary equipment and human resources *(26)*. Cytology screening programmes in many middle-income countries have faced challenges in relation to organization, the extent of population coverage, infrastructure costs, lack of trained staff, and inadequate quality assurance *(28, 29)*.

Table 1: **Prevention of cervical cancer**

Primary prevention:	Current schedules:
Vaccination	Cervarix: females, age 9–14; 2 doses
	Gardasil 4: males and females, age 9–13; 2 doses
	Gardasil 9: males and females, age 9–14; 2 or 3 doses
	Expanded vaccination of adult women - 3 doses regimen
Secondary prevention:	*Papanicolaou* (i.e. cytology)
Cervical screening	Liquid based cytology with Pap stain
	Cytology followed by HPV triage
	HR-HPV primary testing
	HR-HPV primary testing followed by cytology
	Visual inspection options suitable for LMIC: - Acetic acid (VIA) - Lugol's Iodine (VILI) - in combination with HR-HPV testing
Tertiary prevention:	Thermo-coagulation Cryotherapy
Treatment of early disease	LEEP (Loop Electrosurgical Excision Procedure)/ LETZ (Loop Excision of the Transformation Zone)
Treatment of advanced disease	Advanced surgical intervention Chemotherapy Radiotherapy

Low-technology approaches (Including VIA, screen and treat, thermo-ablation)

Different approaches are needed in poor regions of the world. Visual inspection with acetic acid (VIA) is supported by WHO in healthcare settings where HPV testing is prohibitively expensive or where infrastructure or requisite trained professionals are not available *(5)*. Indeed, WHO recommends a strategy of screen with VIA and treatment, over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treatment. In low-resource settings VIA has the attraction of limited additional costs: where basic healthcare services are already in place, essentially it requires 5% acetic acid, cotton wool, gloves, a good light source and a dedicated room to ensure a women's

privacy. With training, VIA can be performed by several levels of healthcare providers, including nurses, midwives and nurse-midwife technicians. Over the last decade the number of LMICs which have adopted VIA testing has increased: as of November 2016, 26 countries have incorporated VIA-based screening into national programmes, with another 30 or so using it within pilot programmes *(30)*. Adoption as national strategy does not always reflect national implementation.

One attraction of VIA is that it permits a single-visit strategy, i.e. a "screen-and-treat" approach where the treatment decision is based on a screening test result and treatment is provided soon or, ideally, immediately after a positive screening test (in contrast to the more conventional approach of cytology, colposcopy, biopsy, and histological confirmation of CIN). In many LMICs where women can travel miles, often on foot, to attend a screening clinic, and where her doing so can impact on her childcare or agricultural responsibilities, screen-and-treat approaches are most likely to promote participation and minimize loss to treatment of a screen-positive woman. There is randomized trial level evidence for reduction in the incidence of high-grade lesions and cervical cancer mortality associated with a single-visit approach with VIA *(31, 32, 33)*.

However, VIA-based screening is acknowledged to be challenging, as the subjective nature of the test can lead to high variability in inter-operator performance, false-positive results, low- to moderate- sensitivity with low specificity, and VIA has poorer performance in post-menopausal women. Thus, VIA screening is recognized as an interim approach in LMIC settings, allowing a supportive screening culture and infrastructure to be set in place until affordable HPV testing can be introduced.

Traditionally, treatment in screen-and-treat programmes has relied on cryotherapy, still the recommended treatment modality in WHO guidance *(5)*. Where available, cryotherapy is an effective treatment. However, in low-income settings the cost and limited availability of carbon dioxide (CO_2) or nitrous oxide (N_2O) gas have led to situations where women have been screened but no treatment is available, unethical in any healthcare context. In recent years there has been renewed interest in use of thermo-coagulation (also known as cold coagulation or increasingly, thermal ablation) to treat cervical epithelial neoplastic (CIN) lesions. A systematic literature review demonstrated equivalent treatment outcomes to cryotherapy *(34)*.

Screen-and-treat approaches in Malawi

Scaling up of quality assured and sustainably resourced VIA screen-and-treat approaches in many sub-Saharan African contexts is still required. Integration of cervical screening provision with reproductive health services, and for HIV positive women with ART services, offers opportunities for consolidation of clinic space, streamlining of health education messages, and best use of over-stretched healthcare workers *(35)*.

We have shown non-inferior outcomes of thermo-coagulation to cryotherapy in a VIA-based screen-and-treat screening service in rural Malawi *(7)*; others have also shown effective treatment in an African context *(36)*. Thermo-coagulation is very suited for use in LMICs, as the machine is lightweight and portable and treatment times at 100°C to 120°C are short and use minimal electricity. The new generation of hand-held thermo-coagulators can be run from solar or battery power and have the potential to transform the ability to provide cervical screening to women in rural sub-Saharan Africa and other resource-constrained settings. WHO is currently reviewing its recommendations on thermo-coagulation (mid-2017).

Awareness of and societal attitudes to cervical cancer in LMICs

Regardless of the approach taken, individual and societal attitudes play a critical role. Typically knowledge and awareness of cervical cancer and cervical screening are low in po or and developing countries, when compared to wealthier regions of the world *(37)*; further, there is often a lack of recognition in LMICs of the important governmental role in initiating cervical screening prevention.

Stigma associated with a cervical cancer diagnosis, fear of the screening procedure itself and of subsequent treatment have also been cited as barriers to screening participation (*38*, *39*). Myths and misconceptions in relation to screening are common. Cultural and religious concerns linked to perceived intrusion of privacy and intimate examination and lack of spousal support together with limited female empowerment, are additional contributory factors to limited engagement with screening even when available *(38, 40)*. Such societal and cultural factors often interact with psychological stressors to influence screening attendance *(41)*. Affordability of testing is another key factor, particularly in poor, rural populations; as is the time that would be taken from other obligations *(42)*.

These barriers constitute an enormous challenge if we are to improve cervical cancer prevention in poor countries such as Malawi. Multi-factorial approaches, combining education, awareness raising and reducing stigma are needed; too often well-intentioned prevention screening efforts fail through a lack of understanding of individual and societal barriers.

HPV vaccination programmes

In 1991, Scottish medical scientist, Professor Ian Frazer and Chinese virologist, Dr Jian Zhou used molecular techniques to develop virus-like particles (VLPs) using only the capsid proteins of HPV *(43)*. VLPs do not contain nucleic acid, and are therefore non-infectious. Two vaccines were quickly developed

and thoroughly tested: Gardasil® from Merck, a quadrivalent vaccine containing HPV 6, 11, 16 and 18 VLPs directed against both genital warts and cervical cancer prevention and Cervarix® from Glaxo Smith Kline, which is a bivalent vaccine containing HPV 16 and 18 VLPs directed solely at cancer prevention. Both vaccines have been in use in different countries since 2006. Both have shown high and sustained efficacy against HPV infections with vaccine types, but it will take many years to show reductions in cancer rates. A nonovalent vaccine Gardasil 9 has recently been licensed through FDA.

Implementation of HPV immunisation programmes in LMICs

Bruni et al *(44)* estimated that 59m women had received at least one dose of HPV vaccine through national programmes in more than 64 countries by 2014. Sadly only 1% were from low- or lower-middle-income countries, demonstrating that populations with the highest incidence and mortality of disease remain largely unprotected. By 2016, over 100 countries had licensed HPV vaccine for use, but how many of these will provide the high coverage needed to ensure effective cancer reduction long term?

Many African countries, have considered HPV immunization and with support from GAVI, have delivered demonstration projects in advance of national rollout. Examples include Rwanda which achieved >90% coverage with three doses of vaccine in 2011 and despite the challenges, has maintained high coverage and set an ambitious goal to eradicate cervical disease by the year 2020 *(45)*. In Malawi, successful demonstrations projects were conducted in the north and south and also reached >90% coverage in schools. However, the challenges of school delivery mean that other outreach settings will be required for national roll-out *(46)*. Tanzania is now in the second year of a demonstration project, delivered in schools by campaign weeks. Malaysia was the first Muslim country to introduce a national HPV immunization programme.

HPV vaccination: challenges for the next decade

The challenges for low- and middle-income countries are substantial, particularly the cost of delivery, even when the cost of vaccine is covered by global arrangements such as the GAVI Alliance. It has been suggested that a five-year delay in introducing the HPV vaccine to LMICs could result in 1.5 to 2 million preventable deaths *(47)*. The greatest global challenge for cervical cancer reduction is therefore a matter of HPV vaccination coverage.

Potential for HPV testing as a primary screening strategy in LMICs

Cervical screening using HPV testing has been shown to give 60–70% more protection against invasive cervical carcinomas than cytology *(48)*. Primary HPV testing could provide an objective, reproducible alternative to subjective and inconsistent VIA screening. In an early study in India, Sankaranaranayan and colleagues in 2004, using the well-established HC2 HPV screening test (Qiagen), concluded further developments were required to make HPV tests more reproducible, less expensive and less sophisticated for them to be feasible and effective in low-resource settings. Almost a decade later, also in India, Joshi et al concluded that HPV testing followed by VIA should be considered if it is affordable *(49)*. A multicentre study from PATH using careHPV® (Qiagen) and our work in rural Malawi using Xpert® HPV (Cepheid) have demonstrated that HPV primary testing is feasible and acceptable to both women and providers *(50, 51)*.

There are however many obstacles. HPV tests themselves are expensive with, to date, a minimum cost of around US$ 6 per test. They also generally require trained laboratory staff and sophisticated equipment for molecular detection, use considerable quantities of plastics and collection media with significant alcohol or formaldehyde content which pose problems for disposal and maintenance/ servicing of equipment can be difficult in areas where companies or their agents are lacking.

The optimal HPV test for LMICs needs to be cheap, require minimal training in its use, and have a quick turn-around, allowing it to be considered as a near patient test *(51)*. Where HPV tests take longer or need to be batched to make effective use of high throughput equipment, a second visit would be necessary for those who are HPV positive. In rural communities with limited transportation options and probably a distant hospital, this is not a priority for asymptomatic woman. A bigger challenge is how to collect a sample for HPV testing. If taking the sample requires a trained healthcare professional, it would be quicker to provide a quality assured VIA screen. There is therefore considerable interest in self-collected specimens. Evidence from Europe has shown this provides an alternative for hard-to-reach and non-attending women *(52, 53)*. This has also been demonstrated in China *(54)*, in Uganda where self- collection-based HR-HPV testing had more than double the uptake of VIA alone *(55)* and in other countries. One limitation of HPV-based screening is the low positive predictive value, since it detects HPV infection not cancer and therefore requires triage of positives to limit false positive and reduce overtreatment.

Nevertheless, self-collected samples with a swab or tampon-like device, in a clinic setting tested locally with a fast, simple HPV test with results being returned to the women while they wait (preferably no more than 1–2 hours), followed by VIA triage and accessible treatment *(7)* must surely be the goal for LMIC to achieve significant population-wide screening and effective reduction in the burden of cervical disease and cancer. That stage has not yet been reached.

Health economic implications

Cervical cancer impacts family, community and national life. A summary of the cost effectiveness arguments in support of the introduction of HPV vaccination and population-wide screening are beyond the scope of this article. Nonetheless, it is important to recognise that such evidence is available. Non-communicable diseases, including cervical cancer, have been shown to adversely affect household income, with LMICs particularly affected *(56)*. A recent systematic review of the economic benefits of vaccines in LMICs reports that the HPV vaccine is cost-effective provided the price per dose is kept below US$150 *(57)*. Another recent comprehensive study uses a model-based approach to estimate the health impact, financial costs and cost-effectiveness of the provision of the HPV vaccine for girls and cervical screening provision for women of screening age. The authors report that HPV vaccination and once in a lifetime screening and treatment were both cost-effective strategies that could avert millions of cervical cancer cases and deaths with substantial DALY savings for relatively modest public health investment compared to overall development assistance health spending *(58)*.

Conclusions

The burden of cervical cancer in Malawi and other LMICs remains unacceptably high. While cytology-based screening has made a very significant impact in western countries, LMICs lack the resource and infrastructure to adopt this approach. Screen-and treat approaches offer an interim solution, and can reach significant numbers of women – there are, however, problems with systematic testing and adequate coverage. HPV vaccination and primary HPV testing offer the prospect of large scale reductions in cervical cancer burden. Governments in countries such as Malawi should aspire to these approaches, with the assistance of the international community. ■

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Professor Heather A Cubie, MBE, BSc, MSc, PhD, FRCPath, FRSE is a retired consultant clinical scientist in virology. She was responsible for training Scottish Clinical Scientists in microbiology from 1994 to 2012; R&D Director in NHS Lothian (1995–2008), Founder Director of the Scottish National HPV Reference Laboratory (2008-2012) and established both the national HPV archive and the Scottish HPV Investigators' Network (SHINe: www.shine.mvm.ed.ac.uk).

She has an Honorary Chair and is a Senior Advisor to the Global Health Academy, University of Edinburgh. In retirement, she is passionate about partnership with Malawian and Scottish colleagues where she has helped establish a sustainable cervical cancer reduction programme.

Professor David Weller graduated from the University of Adelaide in 1982. He undertook PhD studies in Adelaide and Nottingham; after academic posts in Australia he moved to the United Kingdom in 2000 and is currently James Mackenzie Professor of General Practice at the University of Edinburgh. He leads the Cancer and Primary Care Research International Network (Ca-PRI), and is a member of the National Cancer Research Institute Primary Care Clinical Studies Development Group (Foundation Chair, from 2003–2010). He has been involved in cancer screening and early diagnosis research in both Australia and the United Kingdom; he led the evaluation of the United Kingdom pilot of colorectal cancer control, and his group in Edinburgh run a programme of research focusing on the roles of primary care in all aspects of cancer. More recently he has led LMIC programmes, funded by UICC and the British Council, examining early diagnosis and screening in resource-poor settings. David sits on various national and international research and government committees on cancer, and works as a GP in central Edinburgh. He is Co-Director of the University's Centre for Population Health Sciences, and International Dean for SE Asia and Australasia.

References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C et al. GLOBOCAN 2012 v1.1, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2014. Available from: http://globocan.iarc.fr , Accessed on 18 December 2017
2. Global Burden of Disease Cancer Collaboration. The Global Burden of Cancer 2013. JAMA *Oncology* 2015 Jul;1(4):505-27. doi: 10.1001/jamaoncol.2015.0735
3. Ginsburg O, Bray F, Coleman MP, Vanderpuye V, Eniu A, Kotha SR, Sarker M, Huong TT, Allemani C, Dvaladze A, Gralow J. The global burden of women's cancers: a grand challenge in global health. *The Lancet*. 2017 Mar 3;389(10071):847-60
4. Aranda S, Berkley S, Cowal S, Dybul M, Evans T, Iversen K, Moeti M, Osotimehin B, Peterson S, Piot P, Purandare CN, Sidibé M, Trimble T, Tsu VD. Ending cervical cancer: A call to action. *Int J Gynaecol Obstet*. 2017 Jul;138 Suppl 1:4-6. doi: 10.1002/ijgo.12182
5. WHO (accessed July 6th, 2017.)Global Action Plan for the Prevention and Control of Non-communicable Diseases. World Health Organization; 2013 http://www.who.int/nmh/events/ncd_action_plan/en/
6. The Malawi Health Sector Strategic Plan (HSSP) 2011-2016 http://www.medcol.mw/commhealth/publications/3%20Malawi%20HSSP%20Final%20Document%20(3).pdf. Accessed 07/10/2015
7. Campbell C, Kafwafwa S, Brown H, Walker G, Madetsa B, Deeny M, Kabota B, Morton D, Ter Haar R, Grant L, Cubie HA. Use of thermo-coagulation as an alternative treatment modality in a 'screen and treat' programme of cervical screening in rural Malawi. *Int J Cancer* 2016; May 4. DOI:10.1002/ijc.30101
8. Cubie HA, Morton D, Kawonga E, et al. HPV prevalence in women attending cervical screening in rural Malawi Using the cartridge-based Xpert® HPV assay. *J Clin Virol*. 2017

References continued

87:1-4. PMID:27984765

9. Vesco KK, Whitlock EP, Eder M, Burda BU, Senger CA, Lutz K. Risk factors and other epidemiologic considerations for cervical cancer screening: a narrative review for the US Preventive Services Task Force. *Annals of internal medicine*. 2011; 155: 698-705
10. International Collaboration of Epidemiological Studies of Cervical Cancer. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. *Int J Cancer*. 2007 Feb 15;120(4):885-91. Erratum in: *Int J Cancer*. 2007 Jun 1;120(11):2525
11. Trottier H, Franco EL. The epidemiology of genital human papillomavirus infection. *Vaccine*; 2006: 24
12. Schiffman M, Wentzensen N, Wacholder S, Kinney W, Gage JC, Castle PE. Human papillomavirus testing in the prevention of cervical cancer. *J Natl Cancer Inst*. 2011;103: 368-83. PMID: 21282563
13. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends—an update. *Cancer Epidemiology and Prevention Biomarkers*. 2016 Jan 1;25(1):16-27
14. Bosch FX, de Sanjosé S. Human papillomavirus in cervical cancer. *Curr Oncol Rep*. 2002 Mar;4(2):175-83. Review
15. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Cogliano V; WHO International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens--Part B: biological agents. *Lancet Oncol*. 2009 Apr;10(4):321-2
16. de Villiers EM. Cross-roads in the classification of papillomaviruses. *Virology* 2013; 445: 2–10. PMID:23683837
17. Doorbar J, Nagayasu E,Griffin H, Kranjec C, Murakami I. Human papillomavirus molecular biology and disease association. *Rev Med Virol* 2015; 25 Supp S1: 2-23. doi: 10.1002/rmv.1822
18. Denny LA, Franceschi S, de Sanjose S, Heard I, Moscicki AB, Palefsky J. Human papillomavirus, human immunodeficiency virus and immunosuppression. *Vaccine* 2012; 30 Suppl 5: F168-174
19. Crow, JM. HPV: the global burden. *Nature* 2012; 488:S2-3
20. Franceschi S, Herrero R, Clifford GM et al. Variations in the age-specific curves of human papillomavirus prevalence in women worldwide. *Int J Cancer* 2006: 119:2677-2684
21. Vaccarella S, Franceschi S, Engholm G, Lönnberg S, Khan S, Bray F. 50 years of screening in the Nordic countries: quantifying the effects on cervical cancer incidence. *British journal of cancer*. 2014 Aug 26; 111: 965-9
22. Sasieni P, Adams J, Cuzick J. Benefit of cervical screening at different ages: evidence from the UK audit of screening histories. *Br J Cancer* 2003 89: 88–93
23. Peto J, Gilham C, Fletcher O, Matthews FE. The cervical cancer epidemic that screening has prevented in the UK. *Lancet* 2004 364: 249–256
24. Bray F, Loos AH, McCarron P, Weiderpass E, Arbyn M, Moller H, et al. Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. *Cancer Epidemiol Biomarkers Prev* 2005;14:677–86
25. Dowling EC, Klabunde C, Patnick J, Ballard-Barbash R; International Cancer Screening Network (ICSN). Breast and cervical cancer screening programme implementation in 16 countries. *J Med Screen*. 2010;17(3):139-46. doi: 10.1258/jms.2010.010033
26. WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. World Health Organization 2013. http://apps.who.int/iris/bitstream/10665/94830/1/9789241548694_eng.pdf Accessed 18 December 2017
27. Arbyn M, Anttila A, Jordan J, et al., editors. European Commission. In. European Guidelines for Quality Assurance in Cervical Cancer Screening. 2nd edition. Luxembourg: Office for Official Publications of the European Communities; 2008. pp. 1–291
28. Gakidou E, Nordhagen S, Obermeyer Z. Coverage of cervical cancer screening in 57 countries: low average levels and large inequalities. *PLoS Med*. 2008 Jun 17;5(6):e132. doi: 10.1371/journal.pmed.0050132
29. Rodríguez AC, Salmerón J. Cervical cancer prevention in upper middle-income countries. Prev Med. 2017 May;98:36-38. doi: 10.1016/j.ypmed.2016.12.032. Epub 2017 Feb 6
30. Cervical Cancer Action. Global Progress in Cervical Cancer Prevention http://www.cervicalcanceraction.org/comments/maps.php Accessed July 2017
31. Sankaranarayanan R, Esmy PO, Rajkumar R, et al. Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. *Lancet*, 370 (2007), pp. 398–406
32. Denny L, Kuhn L, De Souza M, Pollack AE, Dupree W, Wright Jr TC. Screen-and-treat approaches for cervical cancer prevention in low-resource settings: a randomized controlled trial. *JAMA*, 294 (2005), pp. 2173–218.
33. Shastri SS, Mittra I, Mishra GA, et al. Effect of VIA screening by primary health workers: randomized controlled study in Mumbai, India. *J Natl Cancer Inst*, 106 (2014), p. dju009
34. Dolman et al. Meta-analysis of the efficacy of thermo-coagulation as a treatment method for cervical intraepithelial neoplasia: a systematic review. *BJOG*. 2014 Mar 6. doi: 10.1111/1471-0528.12655
35. Viviano M, DeBeaudrap P, Tebeu PM, Fouogue JT, Vassilakos P, Petignat P. A review of screening strategies for cervical cancer in human immunodeficiency virus-positive women in sub-Saharan Africa. Int J Womens Health. 2017 Feb 2;9:69-79. doi: 10.2147/IJWH.S103868. eCollection 2017. Review
36. Viviano M, Kenfack B, Catarino R, Tincho E, Temogne L, Benski AC, Tebeu PM, Meyer-Hamme U, Vassilakos P, Petignat P. Feasibility of thermocoagulation in a screen-and-treat approach for the treatment of cervical precancerous lesions in sub-Saharan Africa. *BMC Womens Health*. 2017 Jan 7;17(1):2. doi: 10.1186/s12905-016-0355-x
37. Anorlu RI. Cervical cancer: the sub-Saharan African perspective. *Reproductive health matters*. 2008 Nov 30;16(32):41-9
38. Chidyaonga-Maseko F, Chirwa ML, Muula AS. Underutilization of cervical cancer prevention services in low and middle income countries: a review of contributing factors. Pan Afr Med J. 2015 Jul 30;21:231. doi: 10.11604/pamj.2015.21.231.6350. eCollection 2015. Review
39. Lim JN, Ojo AA. Barriers to utilisation of cervical cancer screening in Sub Sahara Africa: a systematic review. *Eur J Cancer Care* (Engl). 2017 Jan;26(1). doi: 10.1111/ecc.12444. Epub 2016 Feb 7. Review
40. McFarland DM, Gueldner SM, Mogobe KD. Integrated Review of Barriers to Cervical Cancer Screening in Sub-Saharan Africa. *J Nurs Scholarsh*. 2016; 48: 490-8. doi: 10.1111/jnu.12232. Epub 2016 Jul 19
41. Williams-Brennan L, Gastaldo D, Cole DC, Paszat L. Social determinants of health associated with cervical cancer screening among women living in developing countries: a scoping review. *Archives of gynecology and obstetrics*. 2012 Dec 1:1-9
42. Aswathy S, Quereshi MA, Kurian B, Leelamoni K. Cervical cancer screening: Current knowledge & practice among women in a rural population of Kerala, India. *The Indian journal of medical research*. 2012 Aug;136(2):205
43. Zhou J, Sun X, Stenzel D, Frazer I. Expression of vaccinia recombinant HPV 16 L1 and L2 ORF proteins in epithelial cells is sufficient for assembly of HPV virion-like particles, *Virology* 1991; 185: 251–257
44. Bruni L, Diaz M, Barrionuevo-Rosas L, Herrero R, Bray F, Bosch X, de Sanjose S, Castellsagué X. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. *The Lancet Global Health* 2016; 4: e453-e463
45. Ministry of Health, Rwanda http://www.moh.gov.rw/index.php?id=34&tx_ttnews%5Btt_news%5D=172&cHash=9b703048f84ed32f9b9231a04655d174 accessed 06/07/17
46. Msyamboza KP, Mwagomba BM, Valle M, Chiumia H, Phiri T Implementation of a human papillomavirus vaccination demonstration project in Malawi: successes and challenges. BMC Public Health 2017; 17: 599-605. DOI 10.1186/s12889-017-4526-y
47. Ferlay, J, Soerjomataram, I, Dikshit, R et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015; 136: E359–E386
48. Ronco G, Dillner J. Elfström KM et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *The Lancet* 2014; 383: 524-532
49. Joshi S, Sankaranarayanan R, Muwonge R, Kulkarni V, Somanathan T, Divate U. Screening of cervical neoplasia in HIV-infected women in India. *AIDS* 2013;27:607–15
50. Jeronimo J, Bansil P, Lim J et al on behalf of START-UP Study Group. A multicountry evaluation of careHPV test¬ing, visual inspection with acetic acid, and papanico¬laou testing for the detection of cervical cancer. *Int J Gynecol Cancer* 2014; 24: 576-85. PMID: 24557438
51. Cubie HA, Campbell C. Use of the GeneXpert test in Malawi. *HPV World* 2017; 1:14-16. www.hpvworld.com
52. Szarewski A, et al. HPV self-sampling as an alternative strategy in non-attenders for cervical screening – a randomised controlled trial. *Br J Cancer* 2011; 104:915-20
53. Snijders PJF, Verhoef VMJ, Arbyn M et al. High-risk HPV testing on self-sampled versus clinician-collected specimens: A review on the clinical accuracy and impact on population attendance in cervical cancer screening. Int J Cancer 2013; 132: 2223–2236. DOI: 10.1002/ijc.27790 Suppl S1-15Szarewski A, et al. HPV self-sampling as an alter¬native strategy in non-attenders for cervical screen¬ing – a randomised controlled trial. *Br J Cancer* 2011; 104:915-20
54. Zhao FH, Lewkowitz AK, Chen F, et al. Pooled analysis of a self-sampling HPV DNA test as a cervical cancer primary screening method. *J Natl Cancer Inst* 2012; 104: 178–88
55. Moses E, et al. Uptake of community-based, self-collected HPV testing vs. visual inspection with acetic acid for cervical cancer screening in Kampala, Uganda: preliminary results of a randomised con¬trolled trial. *Tropical Medicine & International Health* 2015; 20:1355-13
56. Jaspers L, Colpani V, Chaker L, van der Lee SJ, Muka T, Imo D, Mendis S, Chowdhury R, Bramer WM, Falla A, Pazoki R, Franco OH. The global impact of non-communicable diseases on households and impoverishment: a systematic review. *Eur J Epidemiol*. 2015 Mar;30(3):163-88. doi: 10.1007/s10654-014-9983-3. Epub 2014 Dec 21. Review
57. Njau JD, Cairns LK. A literature review on the economic benefits of vaccines in low and middle income countries: Evaluating progress in the era of 'a decade of vaccines' initiative. *Vaccine Reports* 2016: 62-76
58. Campos NG, Sharma M, Clark A, Lee K, Geng F, Regan C, Kim J, Resch S. The health and economic impact of scaling cervical cancer prevention in 50 low- and lower-middle-income countries. Int J Gynaecol Obstet. 2017 Jul;138 Suppl 1:47-56. doi: 10.1002/ijgo.12184

IMPLEMENTING A CERVICAL CANCER PREVENTION SERVICE PLATFORM IN ZAMBIA, FROM SCRATCH

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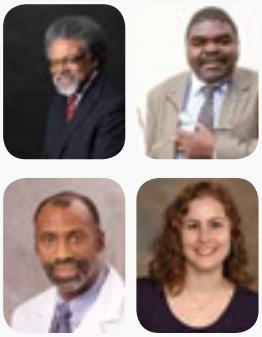

Through shared leadership, unyielding commitment and respect for local beliefs, we built – from scratch – a women-centric cervical cancer prevention infrastructure in Zambia. Startup financing was obtained by highlighting cervical cancer as an AIDS-defining disease and the importance of preventing deaths in women living longer with antiretroviral therapy. Myths were dispelled using culturally-informed community education. The human resource gap was narrowed and the cancer care pathway compressed using a platform of affordable technology and task shifting.

Cervical cancer is a major cause of cancer-related morbidity and death in low- and middle-income countries (LMICs). Although theoretically a preventable disease, implementation and scaling of effective prevention service platforms in these environments is difficult, due mostly to human resource, infrastructural and financial requirements *(1)*. Overcoming these obstacles demands innovative approaches informed by knowledge of the overarching sociocultural context in which the disease occurs, an understanding of the operational nature of fragmented public healthcare systems, and an appreciation of how chronic economic depravity impacts human behaviour.

Background

In 2003, two United States gynaecologic oncologists (MH and GP) visited the University of Zambia Teaching Hospital, the nation's only state-run tertiary level healthcare facility, to assess the status of gynaecologic oncology care in general and the level of cervical cancer screening in particular. The visit was hosted by Friends of Africa, Inc., a non-profit United States-based organization *(2)*, and the Center for Infectious Disease Research in Zambia (CIDRZ), a Zambian non-governmental organization led by a small group of American obstetricians/gynaecologists and Zambian nationals *(3)*. Through a week-long series of formal conferences, informal discussions, clinical ward rounds and social gatherings, we learned first-hand of the human devastation caused by cervical cancer in a large, high-risk, economically marginalized, unscreened population, and the effects of human immunodeficiency virus (HIV)-induced immunosuppression on the natural history of the disease and its outcomes *(4, 5)*. A rapid assessment of the status of cervical cancer control activities in Zambia at that time revealed only 10,000 women had ever been screened by Pap smear since 1964. There were no facilities for radiation therapy, very limited access to chemotherapy, no formally trained oncologists, and woefully inadequate pathology services as there was only one cytology technician and one cytopathologist employed in the public sector, serving a population of 12 million people. Although Zambian colleagues enthusiastically embraced the idea of cervical cancer screening, its benefits in women with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) were felt to be questionable, as their usual course was rapid death soon after diagnosis, long before cervical cancer could develop and progress *(6)*.

Preliminary activities

In the sphere of addressing the HIV/AIDS epidemic globally,

advocacy to increase access to antiretroviral therapy (ART) worldwide was crystallized with the inception of the Global Fund to Fight AIDS, Tuberculosis and Malaria in 2001 *(7)* and the United States President's Emergency Plan for AIDS Relief (PEPFAR) in 2003 *(8)*. Both responses represented large political and financial commitments to the mitigation of HIV/AIDS worldwide through support of programmes targeting HIV and AIDS prevention, treatment, care and support, and health systems strengthening. In combination with the Doha Declaration in 2001 *(9)*, which allowed developing countries to manufacture generic medications to combat public health crises like HIV, global access to ART was accelerated. However, despite longer lifespans as a result of ART, HIV-infected women continue to be at an elevated risk for the progression of human papillomavirus (HPV)-induced cervical cancer precursors to invasive cancer *(10-13)*. There was no specific funding for cervical cancer prevention or treatment in these large global health initiatives as data was lacking on background disease prevalence, rates of progression, and accuracy of screening tests in this high-risk population, despite the fact that cervical cancer had been classified as an AIDS-defining disease by the United States CDC in 1993 *(14)*. Neither were there clear cut guidelines for screening this subpopulation of women, particularly those who lived in resource-constrained nations, like Zambia.

In 2004, with the goals of developing and evaluating the appropriateness of cervical cancer screening protocols for HIV-infected women living in resource-constrained nations, and determining background disease prevalence, we undertook a pilot feasibility study among HIV-infected women attending the University of Zambia Teaching Hospital for HIV care and treatment. Under the auspices of a small (US$ 25,000) grant from the University of Alabama in Birmingham Center for AIDS Research, we screened a cohort (n=150) of women using liquid-based monolayer cytology. The prevalence of squamous intraepithelial abnormalities on cytology was 76% (114/150), of which 32.6% (49/150) were high-grade lesions (HGSIL) and 20% (30/150) suspicious for squamous cell carcinoma (SCC) *(15)*. At the time that these results were published they were among the highest abnormal cervical cytology rates ever reported in the literature *(15)*. They were also some of the very first data demonstrating the need for routine cervical cancer screening of HIV-infected women, as a significant percentage of our cohort either had cancer or precursor lesions, and most (80%) were ART-naïve and seeking treatment for the first time. Data from the study was used to leverage financial support from PEPFAR, through the Centers for Disease Control (CDC), for routine cervical cancer screening of HIV-infected women in Zambia. Immediately after funding was granted (2005) we formed a partnership with the Zambian Ministry of Health, creating the Cervical Cancer Prevention Program in Zambia (CCPPZ) utilizing a low-cost cervical cancer screening intervention called visual inspection with acetic acid (VIA) to be delivered by nurses in cervical cancer prevention clinics tightly linked to PEPFAR-supported public HIV/AIDS care and treatment infrastructures. CCPPZ was the first and largest PEPFAR-supported VIA-cryotherapy based "screen-and-treat" cervical cancer prevention initiative linked to HIV/AIDS care and support programmes in the developing world *(16, 17)*. Inspired by the success of CCPPZ *(16, 18)* and other PEPFAR-supported initiatives, the United States State Department announced the launch of the Pink Ribbon Red Ribbon® campaign on September 2011 to expand "the availability of vital cervical cancer screening and treatment—especially for high-risk HIV-positive women—and also promoting breast cancer education" (19). Launched in Lusaka, CCPPZ was designated as PRRR's flagship programme. In subsequent years, multilateral support for cervical cancer prevention in LMICs has expanded to include support from World Bank and Global Fund and many others.

Reflections

A retrospective evaluation of CCPPZ's "ground-up" modus operandi and its activities, since its inception, suggests several critical aspects that contributed to the success of its initiation, scale-up and sustainability.

1. We leveraged the momentum, infrastructure and capacity-building capabilities of a large and critical global health initiative.

- By initially focusing programmatic activities on high risk HIV-infected women, we acquired the resources needed to initiate a programme to prevent a co-morbid condition – cervical cancer – and the time required to make programmatic adjustments and generate evidence of its value *(17)*. Piggybacking cervical cancer prevention services on a pre-existing PEPFAR-supported HIV Care and Treatment infrastructure through CIDRZ provided an affordable opportunity to utilize the latter's administrative resources, information technology system, office space, management expertise, data management capabilities and approaches to problem solving, as well as its credibility in the larger healthcare space.

2. We chose a prevention intervention that was contextually appropriate and patient-centred.

- The choice of VIA as the primary screening test was a practical decision, based on prevailing circumstances. Although World Health Organization (WHO) endorsement of this screening modality for resource-constrained environments was not to come until 2013, observational studies and field demonstration projects in LMICs had already shown that it was safe, feasible, acceptable, and

could reduce cervical cancer incidence and mortality rates *(20-22)*. Two of us (GP, MH) were experienced colposcopists and thus very familiar with the application of acetic acid to the cervix as a step in the evaluation of abnormal Pap smears. The severe shortage of physicians in Zambia and the fact that VIA could be readily mastered by non-physician providers, prompted us to task-shift the prevention activities from doctors to nurses, the latter of which were much more abundant in number. As a screening test VIA results are rendered in two-three minutes, facilitating immediate treatment (cryotherapy, cold coagulation, LEEP), thereby reducing the need for multiple visits and the subsequent possibility of loss to follow prior to definitive treatment, in a relatively low-cost single-visit "see-and-treat" approach.

- Naked-eye VIA lacks the ability to evaluate certain vascular changes in cervical lesions that may reflect malignant transformation (e.g., coarse punctations or/and mosaicism), yet colposcopy equipment was too expensive. As an alternative we taught screening nurses how to use a commercially available digital camera to capture images of the cervix (digital cervicography) during the screening examination, project and magnify them on a bedside monitor/ television screen located in the clinic. Digital images were discussed with each client for purposes of education and to help dispel prevalent myths and misconceptions about the origin and nature of cervical neoplasia *(23)*. If nurses needed expert consultation to help interpret the findings they could download the images and email them though a locally produced web-based consultation portal, to one of several gynaecologic experts, for immediate distance consultation. This provided nurses with expert back-up and prevented patients from having to make subsequent visits to the clinic prior to receiving a definitive assessment. Each week all digital images were reviewed by the CCPPZ team. Harnessing the power of mobile technology (digital cervicography, web-based consultation) to facilitate communication between nurses in the field and physician-consultants at the university improved the accuracy and efficiency of clinical decision-making. It also facilitated the scale of standardized, quality-assured, cervical cancer screening and real-time distance consultation to all provincial and large district hospitals across Zambia, where it would never have been possible before *(24, 25)*.

3. We overcame the inertia associated with taking the "first step" and strengthened the existing healthcare delivery system along the way.

- The CCPPZ leadership team made a joint decision to start the Program with meagre resources and build as we proceeded, rather than wait until we had developed all of the necessary systems, human capacity and financing. Some of the major problems we confronted and the home grown solutions we developed are demonstrated in a table entitled "Critical Problems and Practical Local Solutions in the Cervical Cancer Prevention Program in Zambia" *(26)*. These approaches to problem-solving provide valuable practical examples for implementing similar programmes in resource-constrained settings. They reflect the product of critical thinking by a very close knit team of pragmatic clinicians (doctors, nurses, public health practitioners), consisting of Zambian nationals and an expatriate United States board-certified gynaecologic oncologist (GP) living within the country, representing the creative process involved in the development of local solutions for local problems instead of transplanting ideas effective in different environments but locally inappropriate.

4. We integrated the Program within preexisting government-operated healthcare infrastructures.

- A significant proportion of the female population in Zambia receive their healthcare through government-operated clinics in which most services are delivered free of charge to patients. Although chronically plagued with inefficiencies due to shortages of mid/high-level personnel and underfinancing, these facilities provide access to the target population and their involvement is critical as a bridge to the eventual institutionalization of cervical cancer screening as a routine healthcare service. After gaining permission from appropriate Ministry of Health officials at the national and local levels, we personally visited each clinic in Lusaka in which we implemented the first sets of "screen and treat services", accompanied by the Director of Lusaka Public Health Services (Dr Moses Sinkala, deceased). During these visits we consulted with the nurse-in-charge of each facility and explained the Program and its purpose in detail, after which arrangements for implementation were made. Improvements to the infrastructure of clinics from our programme's funds benefited the general healthcare infrastructure. Using this approach gave the Program access to physical space, utilities, maintenance, waste disposal and medical/pharmacy services for patients, and ease of referral to and from other departments within the health facilities. It also aided significantly in the transition of our activities from "special project" to "routine service", eventually paving the way for government takeover and ownership which occurred in 2015.

5. We designed the programmatic infrastructure in accordance with the natural history of the target disease.

- Implementation of services for the early detection of cervical cancer, particularly among populations of previously unscreened women in high HIV prevalence environments, uncovers cervical abnormalities ranging from simple and complex precancerous (cervical intraepithelial neoplasia) lesions to advanced stage invasive cancer. From the outset we trained nurses to treat simple precancerous lesions with cervical ablation (cryosurgery and thermocoagulation) and complex ones with surgical excision (loop electrosurgical excision procedure – LEEP) *(27)*, both in outpatient settings. In doing this, we ensured treatment of the full spectrum of precancerous lesions was feasible within the context of a "screen and treat" algorithm. Screening nurses were also trained to perform punch biopsy on lesions that were suspicious for invasive cancer and refer them for appropriate treatment. During the early phase of the Program the vast majority of cervical cancers detected were advanced stage, but as the years progressed and more women accessed screening earlier, the percentage of early stage cancers shifted from 24% to 42%, many of which could be treated and cured with radical surgery alone, if properly performed *(26)*. In response to this change we (GP, MH, MM) implemented a training programme for the surgical treatment of early stage invasive cervical cancer in the Department of Obstetrics and Gynaecology at the University of Zambia Teaching Hospital. Additionally, the leadership of the hospital's Department of Obstetrics and Gynaecology created a Gynaecologic Oncology Unit (headed by MM) to improve the care of women with gynecologic malignancies and the surgical training of registrars. We formed tight linkages with the government's newly established (2006) national cancer centre in Lusaka (Cancer Diseases Hospital) for referral and treatment of women with advanced stage invasive cervical cancer for treatment with chemoradiotherapy.

6. We constantly refined Program operations.

- From the inception of CCPPZ, community education was a centrepiece, as cervical cancer and its prevention/treatment methods are surrounded by myths and misconceptions. We assessed local perceptions of cervical cancer, screening and treatment in a door-to-door community-based initiative *(21)* and used them to shape the content of the messages delivered by peer educators to improve uptake of services. As our appreciation of the impact of "folk beliefs" deepened we opened up a collaboration with the newly formed Ministry of Chiefs and Traditional Affairs to engage local traditional tribal chiefs, traditional marriage counsellors and traditional healers as primary advocates for screening *(28)*. We also employed street-theatre skits throughout Lusaka to disseminate messages about the importance of cervical cancer screening and to challenge the common belief that cancer has spiritual origins.
- When informed by screening nurses and peer educators of the growing demand for screening services by non-HIV infected women, we rapidly extended them to the general population of women in the community, regardless of HIV status. We offered HIV counselling and testing to all women attending screening clinics. These policy changes had the collateral effect of transitioning a service platform built initially for a small but important sector of the population, to a general population-based cervical cancer prevention programme.
- As our need for histopathology services increased we supported public sector pathology services through bulk purchases of supplies (wax, stains, glass slides, ethanol, etc.) and equipment (microscopes, microtomes, etc.). We also negotiated discounted pricing for private sector histopathology services.
- We established a data collection system that allowed us to constantly assess all programmatic phases through a rigorous process of monitoring and evaluation of interim outcomes. Our use of routine programmatic indicators (e.g., screening uptake rates by age and HIV status, rates of cryotherapy-ineligible lesions, screening positivity and CIN2+ detection rates by age and HIV status, rates of "same- day services" and "appropriate referrals") provided ongoing evidence on the role of improvements in the quality of screening and treatment services over time *(29)*. We utilized programmatic data and modeling techniques to learn, for instance, that one case of high-grade cervical intraepithelial neoplasia (CIN 2/3) was detected for every 100 women screened; one case of cervical cancer was detected for every 145 women screened; one case of cervical cancer was prevented per 46 HIV-infected women screened *(26, 30)*. These process and outcomes indicators were among the only clinical effectiveness metrics in the absence of a well-functioning population-based cancer registry and/or a widely-used national-level citizen identification system to measure declines in cancer incidence over time.

7. We emphasized the importance of personal sacrifice for the benefit of the enterprise.

- Building a cohesive team of individuals committed to improving cancer care, from the ground up, in an environment of very limited resources and low financial

remuneration required a remodelling of their outlook to embrace the belief that personal sacrifices in the present can fuel expansive development of the enterprise in the future. We used our weekly digital image review team meetings to emphasize the importance of patient-centred care, efficiency, teamwork, transparency, quality, reliability, personal responsibility, and, most of all, personal sacrifice as investments for future growth of the enterprise, from which each individual would eventually benefit.

Summary

Like any small business startup, we had a vision of the enterprise (women-centric "screen and treat cervical cancer prevention services"), where we wanted to establish it (Zambia), and the customer base (marginalized, unscreened HIV-infected women). Accordingly, we designed the product (digital cervicography, web-based consultation, immediate treatment with outpatient ablation/excision and referral for surgery or chemoradiation) to facilitate efficiency, quality control, monitoring and evaluation. We determined how the product should be marketed (nurse-led service platform to prevent cervical cancer in HIV-infected women, offered in government-operated public health clinics in Lusaka) in accordance with the overarching sociocultural and economic context. After securing a financial investor (PEPFAR) we piloted the enterprise in a few sites, utilizing a culturally-informed marketing strategy (peer educators, traditional chiefs, marriage counselors, healers) to dispel misconceptions about its intent and increase uptake. Through routine feedback from customers and employees, we refined the product as we went along (extended services to all women regardless of HIV status). We added value to the general healthcare environment in which we worked by sharing resources when appropriate (support for pathology services). As a result of our successes and progress, a larger investor (Pink Ribbon Red Ribbon) invested heavily in the enterprise by leveraging even more funding from the initial investor (PEPFAR), thereby facilitating scale-up to all of the country's provincial and large district hospitals, and global recognition of the enterprise and its product. As often happens, an even larger entity (Zambian Government) eventually absorbed the enterprise, leading to its institutionalization and thereby improving the chances of long-term sustainability. ■

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References

1. Gakidou E, Nordhagen S, Obermeyer Z. Coverage of cervical cancer screening in 57 countries: low average levels and large inequalities. *PLoS Med.* 2008; 5:132..
2. Available from http://www.thefriendsofafrica.org
3. Available from http://www.cidrz.org
4. Chirenje ZM. HIV and cancer of the cervix. *Best Pract Res Clin Obstet Gynaecol*. 2005 Apr;19(2):269-76. Review
5. Anorlu RI. Cervical cancer: the sub-Saharan African perspective. *Reprod Health Matters*. 2008 Nov;16(32):41-9. Review
6. Franceschi S, Jaffe H. Cervical cancer screening of women living with HIV infection: a must in the era of antiretroviral therapy. *Clin Infect Dis*. 2007; 45:510–513.
7. Available from http://www.theglobalfund.org
8. The President's Emergency Plan for AIDS Relief: Five-Year Strategy. USAID: PEPFAR; Available from http://www.state.gov/documents/organization
9. World Trade Organization (2001, 20 November) Declaration on the TRIPS agreement and public health, global access to life saving antiretroviral therapy accelerated.
10. Sun XW, Kuhn L, Ellerbrock TV, Chiasson MA, Bush TJ, Wright TC Jr. Human papillomavirus infection in women infected with the human immunodeficiency virus. N *Engl J Med.* 1997;337:1343–9.
11. Vermund SH, Kelley KF, Klein RS, Feingold AR, Schreiber K, Munk G, et al. High risk of human papillomavirus infection and cervical squamous intraepithelial lesions among women with symptomatic human immuno-deficiency virus infection. *Am J Obstet Gynecol.* 1991;165(2):392-400.
12. Mandelblatt JS, Kanetsky P, Eggert L, Gold K. Is HIV infection a cofactor for cervical squamous cell neoplasia? *Cancer Epidemiol, Biomarkers Prev*. 1999;8(1):97–106.
13. Tate DR, Anderson RJ. Recrudescence of cervical dysplasia among women who are infected with the human immunodeficiency virus: a case-control analysis. *Am J Obstet Gynecol.* 2002;186:880-2.
14. Centers for Disease Control and Prevention (CDC) (1992, 18 December) '1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults 'MMWR Recommendations and Reports 41(17).
15. Prevalence and predictors of squamous intraepithelial lesions of the cervix in HIV-infected women in Lusaka, Zambia. Parham GP, Sahasrabuddhe VV, Mwanahamuntu MH, Shepherd BE, Hicks ML, Stringer EM, Vermund SH. *Gynecol Oncol*. 2006 Dec;103(3):1017-22.
16. Mwanahamuntu MH, Sahasrabuddhe VV, Kapambwe S, Pfaendler KS, Chibwesha C, et al. (2011) Advancing cervical cancer prevention initiatives in resource-constrained settings: insights from the Cervical Cancer Prevention Program in Zambia. *PLoS Med*. 8: e1001032.
17. Mwanahamuntu MH, Sahasrabuddhe VV, Pfaendler KS, Mudenda V, Hicks ML, et al. (2009) Implementation of 'see-and-treat' cervical cancer prevention services linked to HIV care in Zambia. *AIDS*. 23:N1–5.
18. Parham GP, Mwanahamuntu MH, Sahasrabuddhe VV, et al. Implementation of cervical cancer prevention services for HIV-infected women in Zambia: measuring program effectiveness. *HIV Therapy*. 2010;4:713–722.
19. Available from www.state.gov/r/pa/prs/ps/2011/09/172244.htm
20. University of Zimbabwe/JHPIEGO Cervical Cancer Project. Visual inspection with acetic acid for cervical-cancer screening: test qualities in a primary-care setting. University of Zimbabwe/JHPIEGO Cervical Cancer Project. *Lancet* 1999; 353: 869-873.8.
21. Gaffikin L, Blumenthal PD, Emerson M, Limpaphayom K. Safety, acceptability, and feasibility of a single-visit approach to cervical-cancer prevention in rural Thailand: a demonstration project. *Lancet* 2003;361:814-820.
22. Sankaranarayanan R, Esmy PO, Rajkumar R, Muwonge R, Swaminathan R, Shanthakumari S et al. Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. *Lancet* 2007;370:398-406.
23. Chirwa S, Mwanahamuntu M, Kapambwe S, Mkumba G, Stringer JSA, Sahasrabuddhe V, Pfaendler K, Parham GP. Myths and misconceptions about cervical cancer among Zambian women: rapid assessment by peer educators. *Glob Health Promot*. 2010 Jun;17(2 Suppl):47-50.
24. Mwanahamuntu MH, Sahasrabuddhe VV, Pfaendler KS, et al. Implementation of 'see-and-treat' cervical cancer prevention services linked to HIV care in Zambia. AIDS. 2009;23:N1–N5.
25. Parham GP, Mwanahamuntu MH, Pfaendler KS, et al. eC3--a modern telecommunications matrix for cervical cancer prevention in Zambia. *J Low Genit Tract Dis*. 2010;14:167–173.
26. Parham GP, Mwanahamuntu MH, Kapambwe S, Muwonge R, Bateman AC, Blevins M, Chibwesha CJ, Pfaendler KS, Mudenda V, Shibemba AL, Chisele S, Mkumba G, Vwalika B, Hicks ML, Vermund SH, Chi BH, Stringer JS, Sankaranarayanan R, Sahasrabuddhe VV. Population-Level Scale-Up of Cervical Cancer Prevention Services in a Low-Resource Setting: Development, Implementation, and Evaluation of the Cervical Cancer Prevention Program in Zambia. *PLoS One*. 2015;10(4):e0122169.
27. Pfaendler KS, Mwanahamuntu, MH, Sahasrabuddhe VV, Mudenda V, Stringer JSAS, Parham GP. Management of cryotherapy-ineligible women in a "screen and treat" cervical cancer prevention program targeting HIV-infected women in Zambia: Lessons from the field. *Gynecol Oncol*. 2008 Sep;110(3):402-7.
28. Kapambwe S, Parham G, Mwanahamuntu M, Chirwa S, Mwanza J, Amuyunzu-Nyamongo M. Innovative approaches to promoting cervical health and raising cervical cancer awareness by use of existing cultural structures in resource-limited countries: experiences with traditional marriage counseling in Zambia. *Glob Health Promot*. 2013 Dec;20 (4 Suppl):57-64.
29. Mwanahamuntu MH, Sahasrabuddhe VV, Blevins M, Kapambwe S, Shepherd BE, Chibwesha C et al. Utilization of cervical cancer screening services and trends in screening positivity rates in a 'screen-and-treat' program integrated with HIV/AIDS care in Zambia. *PLoS One*. 2013;8:e74607.
30. Parham GP, Mwanahamuntu MH, Sahasrabuddhe VV, Westfall AO, King KE, Chibwesha C, Pfaendler KS, Mkumba G, Mudenda V, Kapambwe S, Vermund SH, Hicks ML, Stringer JS, Chi BH. Implementation of cervical cancer prevention services for HIV-infected women in Zambia: measuring program effectiveness. *HIV Therapy*. Nov;4(6),713-722,2010.

AFRICAN HPV PATHOLOGY AND CONTROL: THE WORK OF THE WAKA NETWORK

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Human Papilloma Virus (HPV)-related disease, such as cervical cancer, is a metaphor for an African healthcare challenge: it stimulates researchers to innovate horizontally, combining existing knowledge into new models. Cervical cancer is disappearing in the western world but is rising in Africa. Key to better access to prevention and vaccination is academic expertise, patients' awareness and education, healthcare providers and political commitment. This is the objective of the WAKA network, the "Wanavyama wa Kudhibiti ya HPV" or "artners in controlling HPV". An overview of current WAKA activities is discussed.

Cervical cancer, the most frequent HPV-associated pathology: A metaphor

Cervical cancer is a metaphor for healthcare access in Africa. Of the yearly 528,000 new cervical cancer diagnoses and 260,000 deaths worldwide in 2012 (Globocan data), 85% of the burden occurs in low- and middle-income countries (LMIC). In 2012, 92,000 new diagnoses were made in Africa alone and 57,000 African woman died as a consequence of the disease *(1)*. The prevalence is rising. In South Africa alone, each day eight women die of cervical cancer. This could rise to 12 by 2025, according to the WHO, if access to prevention and vaccination programmes is not improved *(2)*.

Cervical cancer is caused by persistent HPV (human papilloma virus) infection. HPV 16 and 18 genotypes alone account for 70% of all cervical cancers. Visual, cellular and molecular markers for HPV infection, early indicators of potential cancer development over the next 10 years, exist *(3)*. Cervical cancer is therefore preventable through HPV screening and vaccination *(4)*. What makes HPV screening particularly interesting for Africa is that it takes 10 years or more to develop cancer after a positive test *(5)*.

HPV disease is therefore a metaphor for an African healthcare challenge: it stimulates researchers to innovate horizontally in combining existing knowledge into new models. HPV challenges us to think of doing more with less: less frequent but different screening algorithms, attention to different HPV genome strains, "single step screen and treat" approaches will make a difference in Africa. This calls for attention to truly innovative thinking, research and action on HPV in Africa.

While cervical cancer is slowly disappearing in the western world, it is rising in Africa *(6)*. Even though the overall healthcare challenges in Africa are enormous, this gross healthcare access inequality between western and African geographies cannot be accepted. Cervical cancer in Africa calls on all stakeholders such as patients, healthcare workers, scientists and politicians to act together and to act fast in order to inverse the rising prevalence and give good life back to vulnerable African women in their most productive years of life *(7)*.

Developing HPV screening tools and implementing vaccination strategies that are actionable, affordable and accessible in Africa will lead to better overall medicine and healthcare policies *(8)*. It will improve women's health, which is one of the 17 Sustainable Development Goals of the United Nations *(9)*.

Key to better access to prevention and vaccination programmes is increasing awareness and education with patients and healthcare providers and firm political commitment. The prevention tools are available, it is up to the fine-tuned collaboration of medicine, science and political willingness to reverse the spread of cervical cancer and other

HPV-associated pathologies in Africa.

The WAKA network ("Wanavyama wa Kudhibiti ya HPV" or "Partners in controlling HPV"), a multidisciplinary and multi-site collaborative effort led by the University of Antwerp, Belgium, aims at just this. Driven by six project objectives, WAKA aims at increasing scientific, medical and family care knowledge, and at activating a political will to drive a large-scale HPV screening and prevention programme.

Cervical cancer: Key issues

As cervical cancer is caused by a persistent HPV infection *(10)*, HPV can be screened for and potential pre-cancerous lesions can be treated in time. In Africa, a true "pre-cancer screening" can be developed. This is not systematically happening.

Zooming in on key issues that limit access to and implementation of HPV-related screening and prevention, it is striking that most African women are not aware of screening for precancerous risks. Moreover, the notion of "cancer screening" is not accepted in most African cultures *(11)*. They are aware of HIV however, and live with it, but not of or with HPV. Awareness is a prerequisite to action and is therefore key to HPV prevention programme entry.

The healthcare system (both doctors and nurses) is not widely educated to screen for HPV or the development of precancerous lesions. Moreover, access to screening tools, vaccines and precancerous lesion treatment is most often not available. The healthcare system does not reach the less privileged women.

Although cervical cancer is a leading cause of death in active women, it is not high on the political agenda because of lack of knowledge of the seriousness and prevalence of the disease.

The WAKA Africa HPV Network

Established in 2014 by the University of Antwerp, in collaboration with the Sefako Makgatho Health Science University in Pretoria (then University of Limpopo – Medunsa campus), the WAKA network concentrates on nine African countries with six objectives that address the main concerns listed above.

The six WAKA objectives are to:

1) Share the knowledge amongst the local HPV research communities.
2) Strengthen HPV knowledge and action with researchers, healthcare workers and laboratory physicians.
3) Contribute to improving capacity-related issues, such as setting up a quality-controlled local laboratory, the HPV and STI Reference Lab and Training Centre for Africa, which opened on 27 May 2015 and is operational at the Sefako Makgatho Health Science University (SMU) in Pretoria. This reference lab organises the referral of samples, analysis and transitional management of the lab. It ensures training for interested African partners.
4) Coordinate HPV-related research and PhD projects in Africa.
5) Drive political commitment to action through creating awareness with local policy-makers of the HPV-lab-quality-data paradigm.
6) Anchor its work with international bodies such as the WHO.

Delivering on the WAKA objectives:

Sharing knowledge

WAKA is active in nine African countries: South Africa, Malawi, Zambia, Tanzania, Burundi, Kenya, Democratic Republic of Congo, Uganda and Ethiopia. In the years to come, WAKA aims at strengthening its collaboration with French-speaking African countries.

So far, five WAKA symposia (Pretoria 2014, Johannesburg 2015, Kinshasa 2015, a satellite meeting during the SASGO congress in Vereeniging 2016 and during the IPV meeting in Capetown (March 2017)) discussed the progress of the various research projects in each country. Training on quality issues such as GCP was organised. Clinical trial protocols are shared. In future, the collaboration with the ETICCS group in Heidelberg, Germany, may allow central data processing of African trials.

This shared expertise has been discussed with the international HPV community at the yearly world congress on HPV (HPV 2017) held in Cape Town.

WAKA aims at further strengthening the collaborative efforts by improving centralized quality control, sample analysis on HPV presence and genotype.

Strengthening and coordinating knowledge

WAKA will continue to link up interested researchers from different interested and participating academic collaborations and expand the network to the French-speaking part of Africa. Adding to the scientists and physicians who are already involved in the network, WAKA aims at attracting more (informal) healthcare workers, pathologists and gynaecologists to specifically research and act on HPV in cancer.

Improving capacity

A central HPV analysis and genotyping laboratory has been set up with the help of government and industrial partners. Its goal is to analyse samples sent from studies in other African countries. The laboratory is fully equipped and quality controlled. It provides analysis and quality training to interested African research partners. This is an important step in increasing the learning curve and capacity of performing HPV-related analyses.

Coordination of research and PhD projects

Twelve PhD students in six countries work in multidisciplinary collaboration on different topics in HPV research. For example, in fundamental diagnostic-treatment research, a controlled clinical study is set up in DRC: the KINVAV study (NCT02346227), which aims at evaluating the use of a topical antiviral agent, AV2, during colposcopic examination.

In this research, genotyping studies are conducted on cervical samples to investigate the genotype profile of HPV infections in Africa, which may be different from Western genotype profiles. This information is crucial to validate or correct the vaccination approach in Africa. In a recent addition, 400 cases from invasive cervical cancer were included to look at HPV strain prevalence in cancer, facilitating the discussion of which HPV types really cause cancer besides being "just" present in the population.

Formative social research is held to investigate Knowledge/Attitude and Practice (KAP study) of community-based healthcare providers and patients to understand the social barriers to screening for HPV.

Other projects investigate new screening models for Africa that are scientifically solid as well as actionable in the African context. One project will research a Southern Africa-specific model for a single step cervical cancer screening that will be tested on affordability, accessibility and feasibility with community-based healthcare workers.

These studies will be scalable. They aim at being shared between countries – such as the KINVAV study. This builds on the collaborative nature of all current African research projects, adds to data value and overall quality concern and education.

The PhD promoters are associated with both the local university and to a European WAKA partner. This strengthens the common approach and standardization of the research approach and relevance. Two PhD projects have been completed and successfully defended over the last three years, more will follow in the next few years. One of these PhD graduates is now responsible for the reference and training laboratory.

Political commitment

Africa has an important number of fundamental healthcare problems, such as HIV, tuberculosis and maternal health. In this context, inadequate attention is given to HPV-associated disease – especially cervical cancer. The local researchers will publish their findings and their African context in peer-reviewed journals. This will be leveraged to create more contacts with and between political stakeholders from different countries, sharing facts and findings that challenge the current HPV prioritization. WAKA will defend prioritization of HPV-related pathology, especially cervical cancer.

International healthcare organisations

WAKA has twice presented its achievements, plans and approach to the World Health Assembly of the WHO in Geneva.

WAKA is setting up collaboration agreements with ETiCCS (Emerging Technologies in Cervical Cancer Screening) in Heidelberg, Germany, and with INCTR, the International Network for Cancer Treatment and Research. ETiCCS works with SAP on a cutting-edge cloud-based data capture and data transfer technology. This technology allows for reliable data handling in an internet unstable environment such as Africa. WAKA and ETiCCS aim at bringing self-sampling technology closer to the communities and the homes of people in Africa. As Professor Magnus von Knebel-Doeberitz, the head of ETiCCS stated: "Through the ETiCCS programme, we were able to complement applied medical research around biomarkers with the power of cutting-edge cloud technology to bring co-innovation to Africa in a way which really helps to improve people's lives." This is in full agreement with the WAKA research vision for Africa.

INCTR is a WHO-recognized not-for-profit organization dedicated to helping build capacity for cancer research and treatment in developing countries.

The future for WAKA

The future challenges will be the internal organisation and its collaboration with external partners in order to better the lives of people with HPV-related disease.

Internally, the focus will be to strengthen local research and action in more African countries, with a strong African oversight and with help from European universities. Local researchers and laboratory facilities will be empowered, educated and included in a programme that aims at understanding culture, HPV-specific research, and action (local studies, an African HPV Registry). Researchers will be guided into performing better and more structured research protocols to increase the chance for high-impact publication, the potential for external funding and, in the long run, sustainability.

The researchers will be trained in both quantitative and qualitative methods as well as general research methodology and writing. They will be guided in their contacts with local key stakeholders.

Setting up training, awareness and structures for external quality control will increase the general quality of the central, accredited laboratory.

Externally, the expansion of the WAKA network to collaborate intensely with partners in HPV research and

action will be paramount. Geographically, expansion to French-speaking Africa, and the organisations that operate in those countries, is scheduled. Finally, the recognition by the WHO, the World Bank and other international healthcare organisations may help the WAKA network to achieve an independent status.

Conclusions

The HPV pathology in Africa, with its far-reaching healthcare and social impact, calls on all healthcare workers and research organisations to think in a different way. More has to be done with less in order to save the lives of more women and to reverse the rising trend of HPV-related disease in Africa.

The only structural way to move HPV research to reach its goal in a reasonable time is to collaborate. With each other in a multidisciplinary setting in which stakeholders and organisations aim at the one, single goal that Africa needs: a down to earth innovative approach that brings health to women's homes.

For WAKA, it is a challenge and privilege to be instrumental in that. For which WAKA thanks all those who are involved as funders, collaborators and advocates. Please feel free to join us. ■

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References

1. Mena M, Cosano R, Muñoz J, Bosch FX, Sanjosé SD. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Journal of Cancer.* 2010
2. Viviano M, DeBeaudrap P, Tebeu PM, Fouogue JT, Vassilakos P, Petignat P. A review of screening strategies for cervical cancer in human immunodeficiency virus-positive women in sub-Saharan Africa. *Int J Womens Health.* 2017;9:69-79.
3. Dijkstra MG, Snijders PJ, Arbyn M, Rijkaart DC, Berkhof J, Meijer CJ. Cervical cancer screening: on the way to a shift from cytology to full molecular screening. *Ann Oncol.* 2014;25:927-935.
4. Aggarwal P. Cervical cancer: Can it be prevented. World J Clin Oncol. 2014;5:775-780.
5. Bosch FX, Lorincz A, Muñoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol.* 2002;55:244-265.
6. Williamson AL. The Interaction between Human Immunodeficiency Virus and Human Papillomaviruses in Heterosexuals in Africa. *J Clin Med.* 2015;4:579-592.
7. De Vuyst H, Alemany L, Lacey C et al. The burden of human papillomavirus infections and related diseases in sub-saharan Africa. *Vaccine.* 2013;31 Suppl 5:F32-46.
8. Armaroli P, Villain P, Suonio E et al. European Code against Cancer, 4th Edition: Cancer screening. *Cancer Epidemiol.* 2015;39 Suppl 1:S139-52.
9. Callister LC, Edwards JE. Sustainable Development Goals and the Ongoing Process of Reducing Maternal Mortality. *J Obstet Gynecol Neonatal Nurs.* 2017
10. Sankaranarayanan R, Qiao YL, Keita N. The next steps in cervical screening. Women's Health (Lond). 2015;11:201-212.
11. Chan DN, So WK. A Systematic Review of the Factors Influencing Ethnic Minority Women's Cervical Cancer Screening Behavior: From Intrapersonal to Policy Level. *Cancer Nurs.* 2017

ENDING CERVICAL CANCER IN OUR LIFETIME: THE CONTRIBUTION OF PINK RIBBON RED RIBBON

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Cervical cancer is growing burden on women's health today in low- and middle-income countries. Using existing tools for primary prevention (preventing the disease through vaccination against the human papilloma virus (HPV)) and secondary prevention (reducing the impact of disease by detecting and treating early lesions), along with innovative, cost-effective technologies and strategic partnerships, can save the lives of millions of women. Pink Ribbon Red Ribbon is, an affiliate of the George W Bush Institute, is active in making this happen.

The burden of cervical cancer

Cervical cancer is a growing cause of women's mortality in low- and middle-income countries (LMICs). In 2015, approximately 560,000 new cases of cervical cancer were diagnosed worldwide, with 85% of cases in less-developed regions *(1)*. In 2016, cervical cancer surpassed pregnancy-related complications as a cause of death among reproductive-age women in LMICs *(2)*. The World Health Organization (WHO) projects there will be 609,000 new cases worldwide by 2020 if prevention efforts are not increased *(3)*. Cervical cancer is preventable, with effective and inexpensive tools available, but is one of the two leading causes of cancer deaths in sub-Saharan Africa *(4)*. HIV-positive women have a four-to-five times greater increased risk of developing cervical cancer, making HIV-positive women in sub-Saharan Africa especially vulnerable *(5)*. Cervical cancer poses a potent threat for African women as well as their families: given the onset of the disease in women's prime productive years, the social and economic burden imposed on families can be devastating. The considerable costs of cancer care due to lack of or weak health insurance systems leads to large out-of-pocket payments. Additionally, the stigma associated with cancer leads to late stage-presentation at hospitals, resulting in higher costs and unnecessary suffering.

Pink Ribbon Red Ribbon® (PRRR), an affiliate of the George W Bush Institute, is a global public-private partnership that leads coordinated action to save women and girls' lives from cervical and breast cancer in sub-Saharan Africa and Latin America. PRRR mobilizes resources from governments, multilateral organizations, foundations and corporations and engages with national leaders to build long-term, country-led, sustainable programmes for the control of breast and cervical cancers.

There are tools available today to eliminate cervical cancer deaths in 30 years. Using existing tools for primary prevention (preventing the disease through vaccination against the human papilloma virus (HPV)) and secondary prevention (reducing the impact of disease by detecting and treating early lesions), along with innovative, cost-effective technologies and strategic partnerships, can save the lives of millions of women.

Partnerships

Cervical cancer prevention and treatment involve many disparate parts of the health system. Partnerships are needed in service delivery and beyond to strengthen health systems and ensure women and girls have access to cervical cancer services. Partnerships can be used to raise awareness, more effectively pool and utilize funds, and ensure increased focus on the disease.

Incorporating cervical cancer screening into existing health platforms, such as HIV care and treatment and sexual and reproductive health services, can spur innovative programmes and scalable solutions. For example, PRRR has successfully leveraged funding from the President's Emergency Plan for AIDS Relief (PEPFAR) to include cervical cancer screening and treatment of precancerous lesions in HIV programmes

in Botswana, Ethiopia, Tanzania and Zambia, and will extend to Mozambique and Namibia in 2017. Through the PEPFAR integration model, women's most frequent encounters with the health system are harnessed to provide additional services, saving both time and money for patients, providers, funders and health systems. Significant opportunities exist to integrate cervical cancer screening into reproductive health programming, when women are already at the health centre for other services.

This model has been expanded to the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM). In October 2016, GFATM approved the reallocation of savings from Zambia's HIV programme to fund cervical cancer screening and treatment, making it the first country to successfully reprogramme GFATM HIV resources for cervical cancer control, as allowable per a 2015 board decision to provide support for co-infections and co-morbidities. In April 2017, PRRR and GFATM signed an agreement to help countries allocate funds for cervical cancer control programmes, both in new funding requests and in reallocation of HIV programme savings.

Collecting population-based data on service coverage, morbidity and mortality, and harmonizing patient referral and tracking systems provides information on the quality of cancer services and survival rates. UNAIDS included cervical cancer indicators against which countries are expected to report in its 2017 Global AIDS Monitoring Guidance document *(6)*. By providing tools that align to international guidelines, countries can improve data systems, better monitor their progress, and thereby ensure expansion of prevention and treatment services to those most at risk. Similarly, the "Improving Data for Decision-Making in Global Cervical Cancer Programs" consortium, led by the CDC Foundation, and of which PRRR is a member, is finalizing global toolkits and guidance to enhance the quality, coverage, and scale of interventions against the disease.

Primary prevention

To eliminate cervical cancer, we need to accelerate primary prevention through HPV vaccination coverage in sub-Saharan Africa. About 40% of the total population of the continent is under 15 years of age, and this "youth bulge" is largely within the target age for HPV vaccination *(7)*. This presents an opportunity to achieve a cervical cancer-free generation of African women, and securing the health of this generation is crucial *(8)*.

Currently available HPV vaccines are effective against the HPV types most commonly associated with cervical cancer, specifically types 16 and 18, which are responsible for 70% of cases *(9)*. Recent studies conducted in developed economies showed that high HPV-vaccination population coverage resulted in a 90% decrease in HPV infections *(10)*. Gavi, the Vaccine Alliance, is an international organization that brings together public and private sectors to create equal access to vaccines for children living in the world's poorest countries as defined by GNI (Gross National Income) per capita, according to World Bank data. Through Gavi's support in vaccine procurement and implementation, including negotiating a price of US$ 4.50 per dose for eligible countries, 23 countries in sub-Saharan Africa have conducted or are currently implementing a HPV vaccine demonstration programme, and three countries will have nationwide programmes by 2017 *(11)*. However, Gavi does not cover the full operational and delivery costs for administering the vaccine, which countries are expected to co-finance, and this negotiated rate does not apply to middle-income countries.

PRRR supports HPV vaccination programmes in partner countries through vaccine delivery, cold chain support (an uninterrupted, temperature-controlled system for storage and distribution), technical assistance, and implementation of innovative information and communication strategies to improve uptake of the vaccine. The introduction of a new vaccine is not a one-time event, but a challenging process that includes targeted public awareness and advocacy to policy-makers and gate-keepers; community mobilization and education of parents and their daughters to address concerns on side effects and myths and misconceptions; investments in health worker training and vaccine delivery systems; and infrastructure investments in storage and cold chain support *(12)*. Furthermore, health systems were not originally designed to address adolescent health needs, since they are no longer in the childhood immunization programmes, and not yet in the reproductive age group. To reach adolescents, it is essential to integrate both innovative demand generation and multi-channel school and community-based approaches.

In 2013 in Botswana, a non-Gavi eligible country, PRRR supported a two-year HPV vaccination demonstration project. Due to the successful demonstration, Botswana rolled out its self-funded nationwide programme two years earlier than planned, and to date has fully vaccinated over 71,000 girls by the third year of the nationwide programme. In Zambia, PRRR supported a three-year HPV vaccination demonstration project from 2014 to 2016. An evaluation after the first two years highlighted the need to improve uptake of the vaccine. Health educators were re-trained and a social media campaign to engage the community was launched, contributing to increased acceptance rates in the third year, in which 94% of girls in the target cohort completed their vaccination. Following this accomplishment, Zambia plans to apply to Gavi to support the nationwide roll-out starting in 2018. In both instances, PRRR and partners filled in programme gaps that

were not financially supported through Gavi resources or national budgets, and these complementary activities need to be included in comprehensive vaccination programmes.

Despite these successes and anticipated future reduction of cervical cancer incidence, the impact of HPV vaccination will not be evident for the next one to two decades at the current immunization approach. Women who are currently of reproductive age are not eligible for HPV vaccination and need to be screened for cervical precancer and cancerous lesions.

Secondary prevention

Of cervical cancer cases, 85% occur in LMICs, but evidence shows that 95–99% of women in sub-Saharan Africa have never been screened *(13)*. The WHO recommends a same-day approach for screening and treatment of precancerous lesions in LMICs to reduce loss to follow-up *(14)*. The current standard of care is visual inspection with acetic acid (VIA), during which vinegar is applied directly to the cervix, causing lesions to appear white in colour, followed by treatment through cryotherapy, an ablative treatment to freeze off lesions, or loop electrosurgical excision procedure (LEEP), which involves a small electrical wire loop to remove abnormal cells. Innovations in screening and treatment can increase coverage and protect more women against cervical cancer.

VIA is an inexpensive approach, as it does not require specialized equipment and can be provided by trained non-physician healthcare professionals, but has moderate specificity and sensitivity and depends on the skill and experience of individual providers to identify precancerous lesions *(15)*. HPV diagnostic testing is confirmatory for HPV, and when this objective method is coupled with immediate treatment, reduces the incidence of cervical cancer *(16)*. Pairing HPV testing with digital cervicography, a diagnostic medical procedure in which pictures are taken of the cervix to be submitted for interpretation, enables health workers to more accurately identify lesions that can be treated on-site or referred for LEEP or advanced cancer treatment. HPV diagnostic testing is expected to increase the efficiency of cervical screening programmes by decreasing the number of women that need visual inspection: depending on the general HPV infection rate and HIV prevalence in a population, 15–25% of women screened will test positive for HPV *(17)*. The possibility of self-sampling may also increase access, as many women avoid cervical cancer screening because of concerns about privacy, embarrassment, and pain, without loss in accuracy of the test (18). PRRR is working with partners to pilot HPV testing in Peru and Botswana and digital cervicography in Ethiopia in an effort to increase efficiency and effectiveness of screen-and-treat programmes.

Treatment through cryotherapy, while effective, requires a reliable source of gas. Gas tanks are expensive, heavy and cumbersome in field settings, and can leak significant portions of their volume in transit *(19)*. Gas stock-outs often mean that women must come back for treatment another day. Data from PRRR partners show that about 36% of these women never return. The logistical challenges make scaling cryotherapy difficult in settings with inconsistent supply chains and large distances to cover *(20)*. New devices such as battery-operated thermal coagulators will eliminate the need for gas and other consumables and thereby save money: PRRR partners in Tanzania estimate that a thermal coagulator will pay for itself compared to cryotherapy after screening 816 women, approximately within a year, and eliminate all recurring cryotherapy costs afterwards (*21*). Furthermore, the devices are faster than cryotherapy – each treatment takes about one minute – minimizing waiting time for clients and healthcare providers.

Conclusion

Cervical cancer affects women, their families, and communities, disrupting lives as well as the stability that women often provide as heads of households, economic contributors and caretakers. To achieve reductions in cervical cancer incidence and mortality, the global community cannot continue business as usual. Innovative approaches in service delivery and accelerated adoption and scale-up of new technologies are necessary investments to ensure that women do not die of a preventable cancer.

There are several opportunities to accelerate the progress in cervical cancer prevention, and with strategic investments and partnerships, cervical cancer can be eliminated within a lifetime. However, advanced treatment for cervical cancer remains a significant challenge. Many more investments are needed in research, planning, training, and capital expenditure to provide adequate treatment services for invasive disease. Comprehensive cervical cancer control programmes aim to reduce the burden of disease by reducing HPV infections, access to screen-and-treat for precancerous cervical lesions, and providing timely treatment of invasive disease and palliative care. Through innovative partnerships, these goals can be achieved, but it is critical that the third, and most challenging of these points, is addressed with the same attention as primary and secondary prevention. ■

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References

1. GLOBOCAN, 2008. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed 5/18/17.
2. Tsu VD, Jeronimo J, Anderson BO. Why the time is right to tackle breast and cervical cancer in low-resource settings. Bulletin of the World Health Organization 2013; 91:683-690.
3. Comprehensive cervical cancer control: a guide to essential practice – 2nd ed. Geneva. WHO. 2014 (http://apps.who.int/iris/bitstream/10665/144785/1/9789241548953_eng.pdf; accessed October 2016).
4. GLOBOCAN, 2008. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed 5/18/17.
5. Grulich, Andrew E., Van Leeuwen, Marina T., Falster, Michael O., Vajdic, Claire M. "Incidence of cancers in People with HIV/AIDS compared with immunosuppressed transplant recipients: A Meta-Analysis." *Lancet* 2007; 370: 59-67.
6. Global AIDS Monitoring 2017, Indicators for Monitoring the 2016 United Nations Political Declaration on HIV and AIDS. UNAIDS 2016 Guidance. Pages: 111, 150, 162, 175.
7. Lin JY. Youth Bulge: A Demographic Dividend or a Demographic Bomb in Developing Countries? Let's Talk Development. *The World Bank*. 05 Jan. 2012. Available from: http://blogs.worldbank.org/developmenttalk/youth-bulge-a-demographic-dividend-or-a-demographic-bomb-in-developing-countries
8. Ibid; Status Report on Adolescents and Young People in Sub-Saharan Africa: Opportunities and challenges (5 – Population Reference Bureau: http://www.prb.org/pdf12/status-report-youth-subsaharan-Africa.pdf)
9. Comprehensive cervical cancer control: a guide to essential practice – 2nd ed. Geneva. WHO. 2014 (http://apps.who.int/iris/bitstream/10665/144785/1/9789241548953_eng.pdf;accessed October 2016).
10. Garland SM, Kjaer SK, Block SL, et al. Impact and Effectiveness of the Quadrivalent Human Papillomavirus Vaccine: A Systematic Review of 10 Years of Real-world Experience. *Clin Infect Dis* (2016) 63(4):519-527.
11. Gavi Human Papilloma Virus support: http://www.gavi.org/support/nvs/human-papillomavirus/; Castro A, Cinà M, Helmer-Smith M, Vlček C, Oghor C, Cazabon D. A case study of Gavi's human papillomavirus vaccine support programme. *Journal of Health Specialties*. 2017; 5:2-7 http://www.thejhs.org/temp/JHealthSpec512-5406382_150103.pdf; Christensen S. Senegal to introduce HPV vaccine to battle cervical cancer. April 2017. http://www.voanews.com/a/senegal-introduce-vaccine-battle-cervical-cancer/3831288.html.
12. Wigle J, Coast E, Watson-Jones D. Human papillomavirus (HPV) vaccine implementation in low and middle-income countries (LMICs): Health system experiences and prospects. Vaccine. 2013 Aug 20; 31(37): 3811–3817. doi: 10.1016/j.vaccine.2013.06.016 http://www.sciencedirect.com/science/article/pii/S0264410X13007858.
13. Catarino, Rosa et al. "Cervical Cancer Screening in Developing Countries at a Crossroad: Emerging Technologies and Policy Choices." *World Journal of Clinical Oncology* 6.6 (2015): 281–290. PMC. Web. 1 June 2017.
14. Comprehensive cervical cancer control, WHO, 2014.
15. World Health Organization, Cervical Cancer Screening in Developing Countries: Report of a WHO Consultation. Geneva: World Health Organization, 2002; Kang LN, Jeronimo J, Qiao YL, Zhao FH et al. Optimal Positive Cutoff Points for careHPV Testing of Clinician-and-Self-Specimens in Primary Cervical Cancer Screening: an analysis from rural China. *J Clin Microbiol* 2014; 52(6): 1954-61.
16. Jeronimo, 2014; Zhao FH, Jeronimo J, Qiao YL, et al.: An Evaluation of Novel, Lower-Cost Molecular Screening Tests for Human Papillomavirus in Rural China. *Cancer Prevention 2013*, Res 6(9).
17. Bruni L, Diaz M, Castellsagué X, Ferrer E, Bosch FX, de Sanjosé S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. *J Infect Dis*. 2010; 202:1789–1799.
18. Rosenbaum AJ, Gage JC, Alfaro KM, Ditzian LR, et al.: Acceptability of self-collected versus provider-collected sampling for HPV DNA testing among women in El Salvador. *International Journal of Gynecology & Obstetrics* 2014, 126(2): 156-160; Labani S and S Asthana: Human papillomavirus viral load on careHPV testing of self-collected vaginal samples vs. clinician-collected cervical samples. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2014, 181: 233-239.
19. Santos CL, Torres J, Sanchez J, et al: Lack of effectiveness of CO_2 cryotherapy for treatment of CIN. *International Journal of Gynaecological Obstetrics* 2004, 87:44-45; WHO: WHO Technical Specifications: *Cryosurgical Equipment for the Treatment of Precancerous Cervical Lesions and Prevention of Cervical Cancer*. Geneva, Switzerland, WHO, 2012.
20. Maza M, Schocken CM, Bergman KL, et al.: Cervical Precancer Treatment in Low- and Middle-Income Countries: A Technology Overview 2016, *Journal of Global Oncology* 00.
21. PRRR, Unpublished.
22. Maza, 2016.

REGIONAL INITIATIVES

DOWNSTAGING BREAST CANCER IN SUB-SAHARAN AFRICA: A REALISTIC TARGET?

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Most breast cancer patients in high-income countries have a good prognosis. However, patients in sub-Saharan Africa (SSA) have poor prognosis largely because of advanced stage at presentation. Current evidence is consistent with the poor breast cancer survival in SSA being largely driven by long delays to diagnosis rather than a higher prevalence of aggressive disease subtypes, indicating that downstaging may be a viable and effective approach to reducing mortality from the disease in the region.

A diagnosis of breast cancer in most high-income countries has extremely good prognosis in the vast majority of women *(1)*, but in many sub-Saharan African (SSA) countries its prognosis is extremely poor *(2–4)*. In most settings at least 25% of women die within two years of diagnosis *(3–5)*. The need to improve survival rates in affected SSA women is unquestionable, but strategies require sound epidemiologic evidence on fundamental features of this cancer, particularly in relation to the well-established heterogeneity of this tumour. Breast cancer comprises several subtypes – the potential to diagnose early will largely depend on the predominant subtypes present.

Herein, we highlight key features of the epidemiology of breast cancer in SSA. We then address the question of whether downstaging (Box), as an essential component of early curative treatment, is a realistic target, by first examining the dominant subtypes in SSA, the challenges in determining them and whether they and/or other factors influence advanced disease stage at diagnosis. These "fundamentals" of breast cancer in SSA would shed light on the potential to improve survival, and lead to today's pertinent question of how to achieve this within resource-limited settings. Throughout, we acknowledge the diversity of SSA populations, culturally, spatially and in access to healthcare.

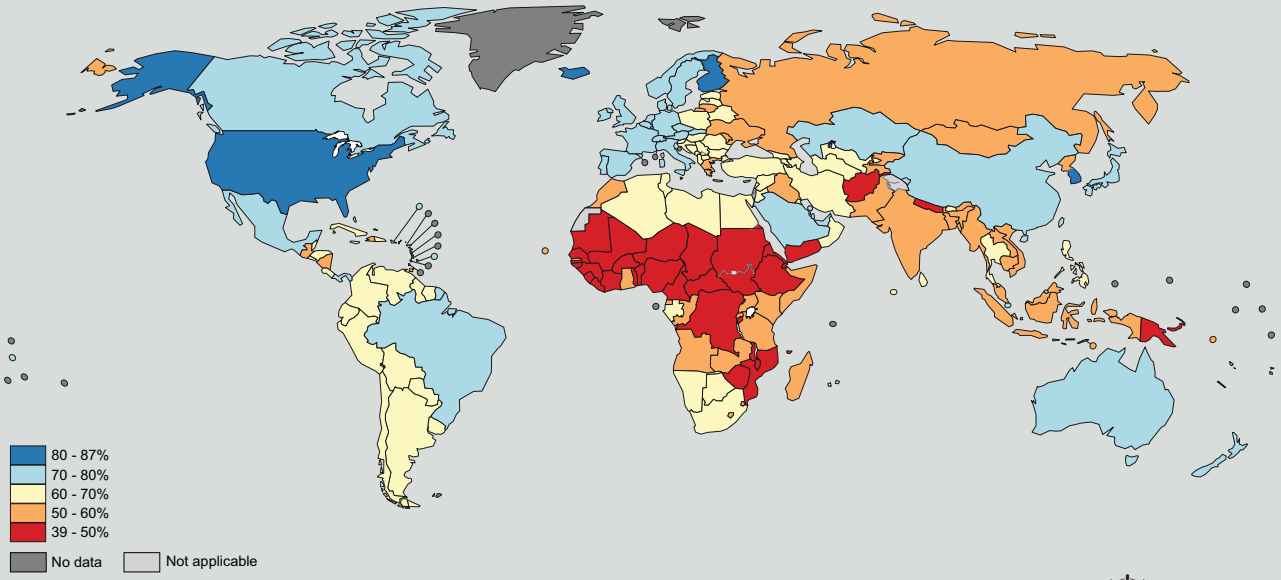
Box: Downstaging symptomatic disease versus screening for asymptomatic disease

- Downstaging, also known as downwards stage migration, refers to the process of ensuring that symptomatic women, i.e. those with a palpable cancer or other clinically-detectable symptom, are diagnosed with earlier, and potentially curable, breast cancer rather than later, mainly incurable, disease.
- Screening aims to detect pre-clinical cancer lesions in asymptomatic women, i.e. women who have no clinically-detectable disease, through the use of mammography, often in combination with other imaging modalities (e.g. ultrasound).

Breast cancer burden in SSA

Like in many other parts of the world, breast cancer is the most common cancer in women in SSA *(6)*. However, in contrast to high-income countries, where in 2012 there was on average one breast cancer death for every four women newly-diagnosed with breast cancer, in SSA this ratio was one breast cancer death for every two new diagnoses, reflecting the poor survival from this disease in the region (Figure 1). In that year 48,000 SSA women died from breast cancer and 94,000 women were diagnosed with breast cancer *(6)*. Future projections of incidence and mortality of breast cancer will depend greatly on SSA's demographic transitions. After retractions at the height of the HIV/AIDS epidemic, today SSA's population growth rates and life-expectancy are increasing at the fastest rates in the world *(7)*. As a consequence, at 2012 age-specific mortality

Figure 1: Five-year breast cancer survival worldwide and in Africa as estimated by its proxy (1- mortality/incidence)



rates, a projected 81,000 breast cancer deaths, that is 11% of global breast cancer deaths will occur in SSA in 2030 *(6)*. This death toll may be higher if there are, as are expected from fertility and lifestyle-related changes, increases in age-specific breast cancer incidence rates, but deaths could be avoided if survival rates are improved.

The SSA-wide picture has considerable between-setting differences. In 2012, estimated incidence rates were highest in South Africa, Mauritius and Nigeria and were at least two-times lower in countries such as Swaziland, The Gambia and Guinea *(6)*. Estimates of incidence time trends are scarce, but the few available – e.g. from Uganda, Malawi and South Africa – show ~5% increases in rates per year *(8–10)*. Poor health information systems have also hindered survival studies. Losses to follow-up of over 40% at three years are common, and this yields very unreliable 5-year survival estimates. For instance, 5-year survival estimates from Ethiopia have ranged from 27% to 46% *(3)*. Nevertheless, five-year survival, as estimated by 1-mortality/incidence *(11)*, also displays regional variations: estimates are higher in Southern Africa than in some Western African populations (Figure 1).

Is breast cancer in SSA a more aggressive disease?

It is often stated that breast cancer in SSA is a more aggressive disease than elsewhere. This perception stems from two main observations. Firstly, the average age at breast cancer diagnosis is ~10 years younger in SSA than in western countries (~50 years in SSA *(6)* vs. 63 years in the United States *(6, 12)*). *This* has been interpreted by some as an indication that the disease in SSA is a more aggressive fast-growing one and of a different fundamental etiological origin. However, as breast cancer incidence rates in young, as in older, age-groups are actually lower in SSA than in high-income countries *(6)*, the shift towards an earlier age at diagnosis is likely to simply reflect the much younger population of the region (~89.4% women in SSA were aged <50 years in 2017 vs. ~57.9% in more developed regions of the world *(13)*). In other words, a larger proportion of breast cancers occur at young pre-menopausal ages in SSA because women in these age-groups represent a larger proportion of the population in that region. Second, most breast cancers in SSA are diagnosed at advanced stages. This then leads to poorer outcomes as treatment options are more limited and less effective. Half of the studies included in a recent systematic review *(14)* reported that 70% or more of breast cancer patients were diagnosed at an advanced stage (TNM stages III and IV *(15)*), and although advanced stage may indicate the predominance of a more biologically aggressive form of disease, it may also be a consequence of long delays between onset of symptoms and diagnosis. These two possibilities are discussed below.

Breast cancer subtypes are usually identified in the clinical setting by immuno-histochemistry (IHC), which stains cancer cells according to the presence of estrogen (ER), progesterone (PR) and human epidermal growth factor-2 (HER2) receptors. ER-positive (ER+) cancers depend on oestrogen for their growth, so they can be treated with drugs to reduce either the effect of this hormone (e.g. tamoxifen) or its levels (e.g. aromatase inhibitors), and usually have a better prognosis *(16)*. Women with HER2-positive (HER2+) cancers have a worse prognosis, but they respond to immunotherapy (i.e.

trastuzumab) in combination with chemotherapy *(16)*. Cancers with no positive ER, PR or HER2 receptors, the so-called "triple negative" cancers, are some of the most aggressive forms of the disease for which there are no targeted treatments *(16)*.

The relative proportions of breast cancer subtypes in SSA are central to the potential for, and strategies needed, to reduce breast cancer deaths in the region. Subtypes differ by environmental and lifestyle risk factors *(17)*, in the contribution of inherited genetic mutations *(18)*, in tumour growth rates pre-diagnosis – the speed of which determines the time window for down-staging – and, post-diagnosis, in disease aggressiveness and prognosis *(19)*, and the choice and costs of targeted treatment modalities *(16)*. If the predominant tumours are aggressive subtypes, the time window for downstaging (i.e. for early diagnosis of symptomatic disease; Box 1) would be short. On the other hand, if the predominant tumours are less aggressive subtypes, the window of opportunity for downstaging may be wider allowing for interventions to accelerate presentation and diagnosis, allowing earlier treatment that may cure the patient or significantly improve quality of life where cure is not possible.

ER+ subtypes account for ~80% of all breast cancers among White women (i.e. those of European ancestry) in the United States, but for a smaller proportion (~65%) among United States Black women *(20)*. In SSA, some studies, albeit not all, have reported lower proportions of ER+ disease *(21)*. These somewhat alarming results from small studies are often quoted, but, as outlined below, the overall picture differs. The reliability of ER testing is highly dependent on the quality of the procedures used for tissue sample collection, fixation, and receptor testing. Poor quality procedures (e.g. delays in processing tissue samples, inadequate fixation and dehydration procedures) lead to false ER-negative results. A recent systematic review *(21)* found marked between-study heterogeneity in the reported proportion of ER+ tumours in the region, with studies based on suboptimal procedures (e.g. archival tissue blocks) yielding lower ER+ frequency estimates whilst those based on better-quality (e.g. prospectively-collected) samples showing that two-thirds of breast cancers in SSA Black women were ER+, a frequency similar to that found among United States Black women. Further, in South Africa, from a nationwide study with receptor testing conducted under the same conditions and in the same laboratories, Black women had only a small excess of ER- disease; percentage of ER- disease was 34% compared to 25% in White women *(22)*. Whilst this difference is important, and needs to be understood, the overlap of subtypes between the groups is notably large: 90% of Black patients have the same breast cancer subtype as their White counterparts.

The systematic review mentioned above *(21)* highlighted the paucity of data on breast cancer subtypes in SSA, cautioning against any generalizations. High-quality procedures for tissue sample collection, processing and receptor testing, are needed for the histological diagnosis and receptor subtyping of breast cancer in SSA. These are already available in Southern Africa, but in Western and Eastern Africa only once this resource is widely available will it be possible to accurately determine the receptor-defined subtype distribution in SSA, and whether it varies across the region. Nevertheless, despite current uncertainties, the existing evidence points to the subtype distribution in many SSA settings not being greatly different from that seen in high-income countries, with most disease being ER+ and, hence likely to be less aggressive, with a long window for downstaging interventions, and potential curability.

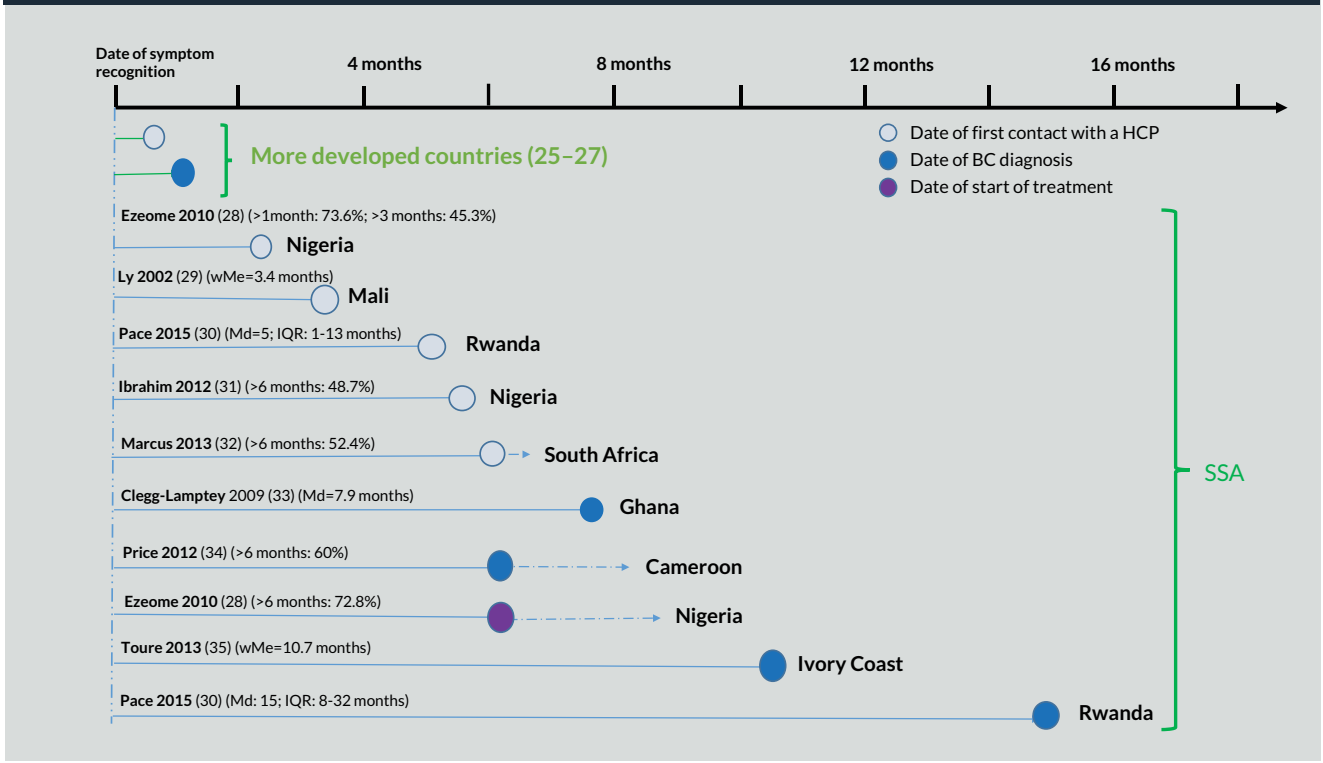
Delays to diagnosis

Time to diagnosis of breast cancer comprises several components. A simplistic partition of this timeline starts at the (unobservable) time from clinical onset of symptoms, i.e. time when lesions become symptomatic and therefore clinically detectable, to their recognition by the woman; the time from symptom recognition to her first contact with a healthcare provider; and the time from first contact with a provider to a definitive diagnosis of breast cancer *(23)*. There is strong evidence that a delay from symptom recognition to diagnosis of more than three months is associated with later stage at presentation and poorer survival *(24)*. In high-income countries, the time interval from symptom recognition to a diagnosis is often less than 30 days *(25–27)*. In contrast, in SSA, these delays are often greater than 6 months *(28–35)* (Figure 2). These long delays are consistent with breast cancers in SSA comprising predominantly slow-growing, less aggressive, ER+ subtypes. Most SSA studies reported average tumour sizes between 4 to 8 cm *(14)*. Tumour growth models *(36)* predict that it would take ~12 and ~22 months for a tumour of 2 cm, the average size when a tumour becomes palpable, to grow to 4 cm and 6 cm respectively (Figure 3). These models are for other populations; nevertheless, their estimates provide a rough indication of the likely duration of the time window for downstaging the disease. Furthermore, reported delay times from SSA studies in Figure 2 are not widely different from model-expected times. This thus suggests a considerable time window representing a realistic opportunity to ensure women receive an earlier diagnosis of palpable disease.

Challenges to early breast cancer diagnosis and treatment

Several studies have shown that early stage breast cancer in SSA *(3–5)*, as elsewhere *(37)*, is associated with better survival

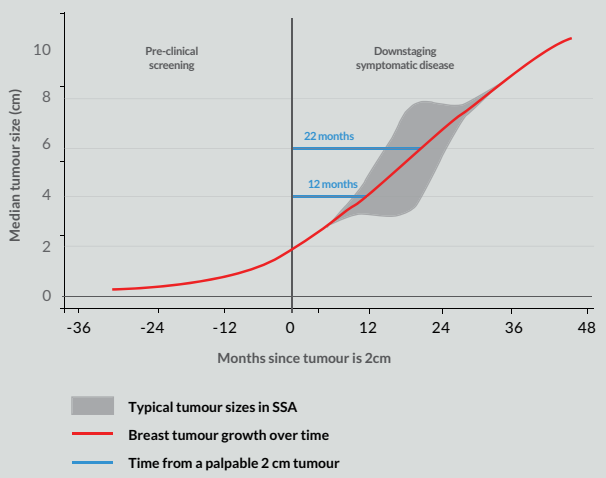
Figure 2: Reported delays in the presentation, diagnosis and treatment of breast cancer in sub-Saharan Africa (modified from Espina et al. *(53)*) and, for comparison, in more developed countries. (IQR: inter-quartile range; Md: median; Me: mean: wMe: weighted mean. A dashed line indicates that the estimate from the original publication shown here is likely to be an underestimation of the true average delay)



than late stage disease, consistent with early diagnosis and treatment leading to reductions in mortality from this disease.

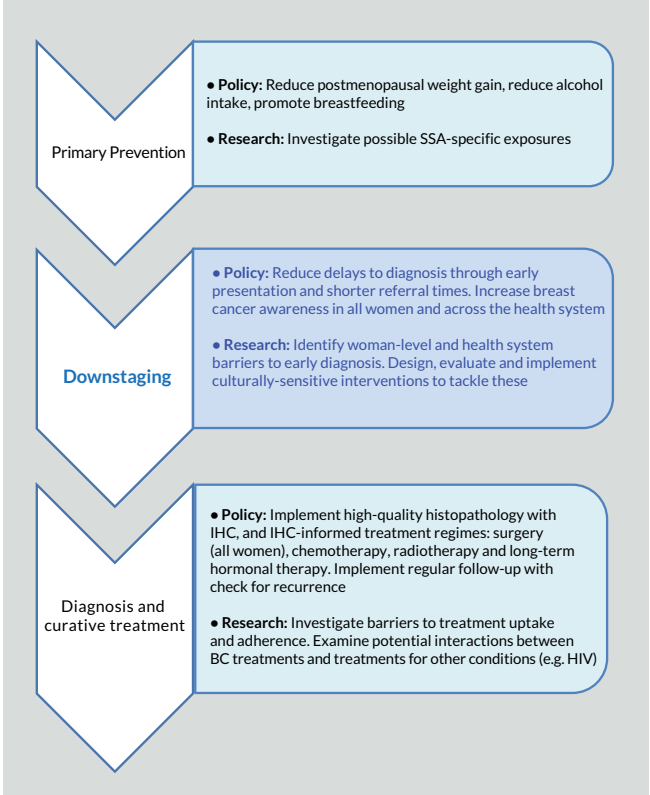
Downstaging of symptomatic breast cancer, rather than screening of asymptomatic women, should be the priority in the region. Mammography screening is advocated for early breast cancer diagnosis in settings where breast cancer stage at diagnosis distributions reflect short intervals between a clinically-detectable symptom (e.g. a palpable lump) and breast cancer diagnosis, and where health systems can support wide-scale screening. Several reasons argue against this approach in SSA settings. Firstly, as the incidence of breast cancer in SSA is lower than in high-income countries, the yield of a screening programme will be low, that is, a large number of women would need to be screened to detect a true case of breast cancer thus shifting the balance between its benefits and harms towards the latter, and reducing its cost-effectiveness. Secondly, the aim of screening is to detect asymptomatic tumours before they give rise to symptoms or become palpable (Box 1); however, substantial delays to diagnosis in SSA occur after a tumour is palpable and, hence, clinically detectable (Figure 2). Thirdly, the implementation and running of a screening programme requires considerable levels of funding, administrative capability as well as infrastructure and technical resources; these are simply not available in low-resource settings such as those in SSA. Fourthly, screening can reduce breast cancer mortality only if women with suspicious

Figure 3: Average modelled breast tumour growth curves in western populations. The long delay times to diagnosis (Figure 2) and the large tumour sizes seen in SSA are not inconsistent with this model



screen-detected lesions, many of which will not be malignant breast cancer, have timely access to appropriate diagnosis and treatment. The addition of women with suspicious screen-detected lesions to those with symptomatic disease would place significant additional burden on already over-stretched healthcare systems in the region. It is worth noting that even in countries with a population-based mammographic screening programme, which has reached a high coverage, the majority of breast cancer patients present symptomatically (e.g. only 32% of all breast cancers in the United Kingdom in 2007 were

Figure 4: Breast cancer control in sub-Saharan Africa: policy recommendations and research priorities (BC: breast cancer; HIV: human immunodeficiency virus; IHC: immuno-histochemistry; SSA: sub-Saharan Africa



screen-detected; 56% among those in the target age-group 50–69 years *(38)*). There is currently no conclusive evidence that screening asymptomatic women with low-technology approaches such as breast self-examination (BSE) or clinical breast examination (CBE) leads to reductions in breast cancer mortality mortality *(39)*, albeit CBE may be useful for downstaging symptomatic disease (as discussed below).

How can downstaging be achieved? The Breast Health Global Initiative and the Breast Cancer Initiative 2.5 recommend a stratified approach, with a phased implementation, for low-resource settings *(40, 41)*. The first phase should focus on tackling health-system related barriers to early diagnosis of symptomatic breast cancer through, the provision of adequate training to healthcare professionals, development of standardized diagnostic and treatment guidelines and protocols as well as implementation of clear patient navigation pathways to ensure faster referral to tertiary care services. Initiatives to increase breast cancer awareness in the population should be promoted in addition to ensuring that the health system will be able to cope with the increasing demand in diagnostic capability that they will generate. Studies in rural Sudan *(42)* and Tanzania *(43)*, as in India *(44)*, have shown that breast cancer awareness campaigns coupled with CBE (performed by trained non-medical volunteers) are effective in downstaging the disease in these settings where the majority of women present with advanced disease. Given that no conclusive evidence currently exists, a pertinent question is whether such downstaging will translate into mortality reductions. Some of these ongoing studies will be able to provide an answer to this question in the near future.

Early diagnosis must be coupled with early treatment if reductions in mortality are to be achieved. As no single subtype is rare in SSA, making IHC routinely available should be a priority unless robust local evidence suggests otherwise. In SSA settings where IHC testing is not available it may be reasonable to assume, on the basis of current evidence, that the majority of patients would benefit from anti-hormonal treatments particularly as they are low cost, easy to administer and have few side effects.

Research priorities for downstaging breast cancer

Research priorities for downstaging need to be established within a broader framework for breast cancer control in SSA (Figure 4). Appropriate recognition of breast cancer symptoms, improved access to health facilities and timely diagnosis of symptomatic patients are essential to downstage breast cancer in SSA. Understanding the influence of the factors that influence a woman's journey to breast cancer diagnosis and treatment is vital to the development of effective interventions. Studies in SSA *(45–47)* have found that delays to diagnosis are associated with a combination of woman-level (e.g. low educational level, poor socioeconomic status, living in a rural area, poor breast cancer awareness, belief in traditional or spiritual medicine) and health system-related factors (e.g. distance to nearest healthcare provider, number of healthcare providers visited prior to diagnosis, health professionals with poor breast cancer knowledge, unavailability of suitable diagnostic facilities, lack of appropriate referral pathways). However, the relative importance of these factors is likely to vary from setting to setting as a result of differences in sociocultural norms, economic development and healthcare systems. This is currently being investigated in the multi-country African Breast Cancer – Disparities in Outcomes (ABC-DO) study, a study on the determinants of breast cancer survival in five SSA countries (Namibia, Nigeria, South Africa, Uganda and Zambia) *(48)*. Findings from this study, which will become available within the next two years, will provide a first indication of the extent to which woman-level and health system barriers to early diagnosis differ across settings in the region, as well as of their impact on stage at diagnosis and survival, and will provide the necessary evidence-base to design appropriate interventions for downstaging breast cancer. Such interventions will need to be properly evaluated not only in terms of their effectiveness in reducing stage at breast cancer diagnosis but, crucially, also on whether they

will ultimately translate into reductions in mortality from the disease.

For downstaging to reduce mortality from breast cancer it needs to be coupled with early treatment. Research on the factors that influence timely access to appropriate treatment regimens, and their uptake and adherence *(49–52)*, is crucial. Accurate determination of the distribution of receptor-defined subtypes of breast cancer across the region should be regarded as a priority. Ideally, high-quality IHC should be available in clinical settings as part of the routine management of breast cancer patients to inform treatment choices but achieving this would not be trivial (e.g. need for well-equipped pathological laboratories, adequately trained technicians and pathologists). In the absence of this, large multi-country studies based on a common high-quality control protocol, which properly addresses the analytical issues which have plagued previous IHC studies, will help to assess the extent to which there is heterogeneity across the region (e.g. by sub-region, ethnicity) and would provide the necessary evidence-base to monitor trends in the subtype distribution as women adopt more westernisced risk profiles (e.g. smaller family sizes, high BMI).

Finally, setting up and maintaining high-quality health information systems is essential for measuring the breast cancer burden in the population, monitoring future trends, and for proper evaluation of interventions that are rolled out into the community. Recent technological developments (e.g. in m-health) may help to achieve this in low-resource settings, particularly for patient follow-up which has been notoriously difficult to implement in SSA settings. ■

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References

1. Allemani C, Weir HK, Carreira H et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet.* 2015;385(9972):977-1010
2. Sankaranarayanan R, Swaminathan, R. Cancer Survival in Africa, Asia, the Caribbean and Central America. Lyon, France: International Agency for Research on Cancer (IARC). *IARC Scientific Publication, No 162*; 2011
3. Kantelhardt E, Zerche P, Mathewos A et al. Breast cancer survival in Ethiopia: A cohort study of 1,070 women. *Int J Cancer.* 2014
4. Gakwaya A, Kigula-Mugambe JB, Kavuma A et al. Cancer of the breast: 5-year survival in a tertiary hospital in Uganda. *Br J Cancer.* 2008;99(1):63-7
5. Galukande M, Wabinga H, Mirembe F. Breast cancer survival experiences at a tertiary hospital in sub-Saharan Africa: a cohort study. *World J Surg Oncol.* 2015;13:220
6. Ferlay J, Soerjomataram I, Dikshit R et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. Lyon, France: International Agency for Research on Cancer; 2013. 2013. http://globocan.iarc.fr [accessed on 1/6/2017].
7. United Nations, Department of Economic and Social Affairs, Population Division. *World Population Prospects: The 2015 Revision, Key Findings and Advance Tables.* Working Paper No. ESA/P/WP.241. 2015
8. Wabinga HR, Nambooze S, Amulen PM et al. Trends in the incidence of cancer in Kampala, Uganda 1991-2010. *Int J Cancer.* 2014;135(2):432-9
9. Misiri H, Dzamalala C, Adriss A et al. Cancer incidence in Malawi: Time trends in Blantyre 1996-2005 and predictions up to 2015. *Global Adv Res J Med and Med Sciences.* 2012;1(6):145-53.

Available from: http://garj.org/garjmms/7/2012/1/6/cancer-incidence-in-malawitime-trends-in-blantyre-1996-2005-and-predictions-up-to-2015#sthash.jFnbJv8p.dpuf.

10. Singh E, Joffe M, Cubasch H et al. Breast cancer trends differ by ethnicity: a report from the South African National Cancer Registry (1994-2009). *Eur J Public Health.* 2017;27(1):173-8
11. Asadzadeh VF, Karim-Kos HE, Janssen-Heijnen ML et al. The validity of the mortality to incidence ratio as a proxy for site-specific cancer survival. *Eur J Public Health.* 2011;21(5):573-7
12. Howlader N, Noone AM, Krapcho M et al. SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Based on November 2015 SEER data submission, posted to the SEER web site. 2015. Available from: http://seer.cancer.gov/csr/1975_2013/ [accessed on 1/6/2017].
13. US Census Bureau. International Programs (https://www.census.gov/population/international/data/idb/region.php?N=%20Results%20&T=10&A=aggregate&RT=1&Y=2017&R=55&C=) [accessed on 1/6/2017].
14. Jedy-Agba E, McCormack V, Adebamowo C, dos-Santos-Silva I. Stage at diagnosis of breast cancer in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Glob Health.* 2016;4(12):e923-e35
15. Edge SB BD, Compton CC, Fritz AG et al. (editors). AJCC Cancer Staging Manual (7th ed.). New York, NY: Springer; 2010
16. Senkus E, Kyriakides S, Ohno S et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2015;26 Suppl 5:v8-30
17. Yang XR, Chang-Claude J, Goode EL et al. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. *J Natl Cancer Inst.* 2011;103(3):250-63
18. Purrington KS, Slager S, Eccles D, Yannoukakos D et al. Genome-wide association study identifies 25 known breast cancer susceptibility loci as risk factors for triple-negative breast cancer. *Carcinogenesis.* 2014;35(5):1012-9
19. Blows FM, Driver KE, Schmidt MK et al. Subtyping of breast cancer by immunohistochemistry to investigate a relationship between subtype and short and long term survival: a collaborative analysis of data for 10,159 cases from 12 studies. *PLoS Med.* 2010;7(5):e1000279
20. National Cancer Institute Surveillance Epidemiology and End Results Program (SEER) http://seer.cancer.gov/data/ [accessed 1/6/2017]
21. Eng A, McCormack V, dos-Santos-Silva I. Receptor-defined subtypes of breast cancer in indigenous populations in Africa: a systematic review and meta-analysis. *PLoS Med.* 2014;11(9):e1001720
22. Dickens C, Duarte R, Zietsman A et al. Racial comparison of receptor-defined breast cancer in Southern African women: subtype prevalence and age-incidence analysis of nationwide cancer registry data. *Cancer Epidemiol Biomarkers Prev.* 2014;23(11):2311-21
23. Caplan L. Delay in breast cancer: implications for stage at diagnosis and survival. *Front Public Health.* 2014;2:87
24. Richards MA, Smith P, Ramirez AJ et al. The influence on survival of delay in the presentation and treatment of symptomatic breast cancer. *Br J Cancer.* 1999;79(5-6):858-64
25. Arndt V, Sturmer T, Stegmaier C et al. Patient delay and stage of diagnosis among breast cancer patients in Germany -- a population based study. *Br J Cancer.* 2002;86(7):1034-40
26. Nosarti C, Crayford T, Roberts JV et al. Delay in presentation of symptomatic referrals to a breast clinic: patient and system factors. *Br J Cancer.* 2000;82(3):742-8
27. Arndt V, Sturmer T, Stegmaier C et al. Provider delay among patients with breast cancer in Germany: a population-based study. *J Clin Oncol.* 2003;21(8):1440-6
28. Ezeome ER. Delays in presentation and treatment of breast cancer in Enugu, Nigeria. *Niger J Clin Pract.* 2010;13(3):311-6
29. Ly M, Diop S, Sacko M et al. [Breast cancer: factors influencing the therapeutic itinerary of patients in a medical oncology unit in Bamako (Mali)]. *Bull Cancer.* 2002;89(3):323-6
30. Pace LE, Mpunga T, Hategekimana V et al. Delays in Breast Cancer Presentation and Diagnosis at Two Rural Cancer Referral Centers in Rwanda. *The Oncologist.* 2015;20(7):780-8
31. Ibrahim NA, Oludara MA. Socio-demographic factors and reasons associated with delay in breast cancer presentation: A study in Nigerian women. *The Breast.* 2012;21(3):416-8
32. Marcus TS, Lunda S, Fernandez L. Delayed breast cancer presentation: hospital data should inform proactive primary care. *Afr J Primary Health Care Family Planning* 2013;5: Art
33. Clegg-Lamptey J, Dakubo J, Attobra YN. Why do breast cancer patients report late or abscond during treatment in ghana? A pilot study. *Ghana Med J.* 2009;43(3):127-31
34. Price AJ, Ndom P, Atenguena E, Mambou Nouemssi JP, Ryder RW. Cancer care challenges in developing countries. *Cancer.* 2012;118(14):3627-35
35. Toure M, Nguessan E, Bambara AT, Kouassi YK, Dia JM, Adoubi I. [Factors linked to late diagnosis in breast cancer in sub-Saharan Africa: case of Cote d'Ivoire]. *Gynecol Obstet Fertil.* 2013;41(12):696-700
36. Weedon-Fekjaer H, Lindqvist BH, Vatten LJ et al. Breast cancer tumor growth estimated through mammography screening data. *Breast Cancer Res.* 2008;10(3):R41
37. Walters S, Maringe C, Butler J et al. Breast cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK, 2000-2007: a population-based study. *Br J Cancer.* 2013;108(5):1195-208
38. Lawrence GK, Kearins O, Lagord C et al. The Second All Breast Cancer Report. Focusing on Inequalities: Variation in breast cancer outcomes with age and deprivation. UK: *National Cancer Intelligence Network* (NCIN), 2011
39. Lauby-Secretan B, Scoccianti C, Loomis D et al. Breast-cancer screening--viewpoint of the IARC Working Group. *N Engl J Med.* 2015;372(24):2353-8
40. El Saghir NS, Adebamowo CA, Anderson BO et al. Breast cancer management in low resource countries (LRCs): consensus statement from the Breast Health Global Initiative. *Breast.* 2011;20 Suppl 2:S3-11
41. Anderson BO, Cazap E, El Saghir NS et al. Optimisation of breast cancer management in low-resource and middle-resource countries: executive summary of the Breast Health Global Initiative consensus, 2010. *Lancet Oncol.* 2011;12(4):387-98
42. Abuidris DO, Elsheikh A, Ali M et al. Breast-cancer screening with trained volunteers in a rural area of Sudan: a pilot study. Lancet Oncol. 2013;14(4):363-70
43. Ngoma T, Mandeli J, Holland JF. Downstaging cancer in rural Africa. *Int J Cancer.* 2015;136(12):2875-9
44. Sankaranarayanan R, Ramadas K, Thara S et al. Clinical breast examination: preliminary results from a cluster randomized controlled trial in India. *J Natl Cancer Inst.* 2011;103(19):1476-80
45. Jedy-Agba E, McCormack V, Olaomi O et al. Determinants of stage at diagnosis of breast cancer in Nigerian women: sociodemographic, breast cancer awareness, health care access and clinical factors. *Cancer Causes Control.* 2017; 28(7):685-97.
46. Brinton L, Figueroa J, Adjei E et al. Factors contributing to delays in diagnosis of breast cancers in Ghana, West Africa. *Breast Cancer Res Treat.* 2017;162(1):105-14
47. Akuoko CP, Armah E, Sarpong T et al. Barriers to early presentation and diagnosis of breast cancer among African women living in sub-Saharan Africa. *PLoS One.* 2017;12(2):e0171024.
48. McKenzie F, Zietsman A, Galukande M et al. African Breast Cancer—Disparities in Outcomes (ABC-DO): protocol of a multicountry mobile health prospective study of breast cancer survival in sub-Saharan Africa. *BMJ Open.* 2016;6(8)
49. Adisa AO, Lawal OO, Adesunkanmi AR. Paradox of wellness and nonadherence among Nigerian women on breast cancer chemotherapy. *J Cancer Res Ther.* 2008;4(3):107-10
50. Anyanwu SN, Egwuonwu OA, Ihekwoaba EC. Acceptance and adherence to treatment among breast cancer patients in Eastern Nigeria. *Breast.* 2011;20 Suppl 2:S51-S3
51. Egwuonwu OA, Anyanwu SN, Nwofor AM. Default from neoadjuvant chemotherapy in premenopausal female breast cancer patients: what is to blame? *Niger J Clin Pract.* 2012;15(3):265-9
52. Oguntola AS, Adeoti ML, Akanbi OO. Non-adherence to the use of tamoxifen in the first year by the breast cancer patients in an African Population. *East Central Afr J Surgery.* 2011;16(1):52-6
53. Espina CM, McKenzie F, dos-Santos-Silva, I. Delayed breast cancer presentation and diagnosis in African women: a systematic review. *Ann Epidemiol* 2017;27(10):659-671.

CANCER PREVENTION AND CONTROL IN THE CARIBBEAN

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Objective: To describe the status, progress and challenges to implementing cancer interventions in the Caribbean.

Methods: Data on cancer mortality, policies and services were extracted from Pan American Health Organization (PAHO) databases, government and non-governmental websites and the peer-reviewed literature.

Results: Cancer is the second leading cause of death; plans are in place in most countries, screening services exist in several countries, but significant gaps remain in treatment and palliative care. Conclusion: Multisector collaboration, technical assistance and funding is needed to improve care.

The Caribbean is a sub-region of the Americas, composed of 30 countries/territories which are principally a chain of islands surrounded by the Caribbean Sea. The Caribbean Community (CARICOM) is a grouping of 15 Member States and five Associate Members, and it was the political leadership of this group that led efforts to strengthen the prevention and control of noncommunicable diseases (NCDs), with the 2007 Port of Spain Declaration *(1, 2)*. This called for multisector policies and health system strengthening, among others, to reduce the NCD burden, and in turn spurred the global NCD movement which resulted in the United Nations political declaration on NCDs in 2011 *(3)*. Since then, governments and non-state actors have rallied around the call and intensified interventions to address NCDs, with the goal of a 25% reduction in related premature mortality by 2025 *(4)*.

These commitments have led to a focus on cancer, one of the four main NCDs. Governments throughout the Americas endorsed a PAHO/WHO Regional Plan of Action for the Prevention and Control of Noncommunicable Diseases 2013–2019, which provides the overall framework to address cancer and other NCDs *(5)*. The recommendations include establishing national cancer plans and registries; implementing primary prevention policies (implementation of the WHO Framework Convention on Tobacco Control; regulations to reduce alcohol consumption; policies that support healthy eating, promotion of breast feeding and promotion of physical activity, and HPV and HBV vaccination); creating organized breast and cervical screening programmes; and improving cancer treatment and palliative care services.

While these recommendations have been promoted in various fora, including the recent 2017 World Health Assembly *(6, 7)*, implementation has perhaps not been as comprehensive as needed to ensure sufficient progress towards the overarching NCD goal of reducing premature mortality. In this article, we describe the status, progress and challenges to implementing cancer control interventions in the Caribbean sub-region from the perspectives of an international governmental organization and civil society organization.

Methods

Cancer mortality data were retrieved from the Pan American Health Organization (PAHO) Mortality Database *(8)*. Relevant reports on cancer programmes and initiatives were retrieved from official websites of the PAHO, Caribbean Public Health Agency, CARICOM, Healthy Caribbean Coalition, Port of Spain Declaration Evaluation (Caribbean Unity in Health) and relevant websites from Ministries of Health and cancer societies of the Caribbean. Published articles in peer-reviewed journals were retrieved from a literature search, conducted April–May 2017, using the following search terms "cancer" AND "Caribbean" AND "prevention" AND "screening" AND "treatment". PubMED, Science Direct, and Google Scholar were used, and articles published after 1 January 2008 were considered.

We also extracted relevant data on cancer policies, plans, screening, treatment, palliative care, and cancer registration,

Table 1: **Cancer deaths and related characteristics of selected Caribbean countries *(8)***

Country	Total population (2016)	Gross National Income (US$ per capita, ppp, 2014)	National health expenditure (as %GDP public, 2014)	Total deaths		Total cancer deaths		Male cancer deaths		Female cancer deaths	
				Number of deaths, all causes, both sexes, latest year available	Age-adjusted rates, both sexes, per 1,000 population, latest year avaialble	Number of cancer deaths (% of total deaths) , all sites, both sexes, latest year available	Age-adjusted rates per 100,000 population, latest year available	Total number of cancer deaths , all sites, both sexes, latest year available	Age-adjusted rates per 100,000 population, latest year available	Total number of cancer deaths , all sites, both sexes, latest year available	Age-adjusted rates per 100,000 population, latest year available
Antigua & Barbuda	94,000	21,370	3.8	579	634.2	133 (23%)	145.6	76	175.7	57	118.6
Bahamas	393,000	22,290	3.6	2,065	546.5	411 (20%)	108.8	194	104.9	217	112.4
Barbados	291,000	15,190	4.7	2,488	861.7	558 (22%)	193.2	278	199	280	187.7
Belize	367,000	7,590	3.9	1,587	451.2	186 (12%)	52.9	82	46.7	104	59
Dominica	74,000	10,480	3.8	609	829.1	107 (18%)	145.7	61	164.5	46	126.4
Grenada	111,000	11,720	2.8	868	784.1	171 (20%)	154.5	90	160.6	81	148.2
Guyana	771,000	6,940	3.1	5,544	731	470 (8%)	61.9	199	52.4	271	71.6
Jamaica	2,803,00	8,640	2.8	16,789	609.9	3,400 (20%)	123.5	1,863	136.1	1,537	111.1
Saint Kitts & Nevis	52,000	22,600	2.1	341	672.2	63 (18%)	124.2	33	130.2	30	118.2
Saint Lucia	164,000	10,540	3.6	1,293	791.5	246 (19%)	150.6	146	183.3	100	119.4
St Vincent & the Grenadines	102,000	10,730	4.4	875	852.6	185 (21%)	180.3	112	214.7	73	144.6
Suriname	548,000	17,040	2.9	3,130	581.5	432 (14%)	80.26	240	88.9	192	71.5
Trinidad &Tobago	1,365,00	31,970	2.9	10,203	768.2	1650 (16%)	124.2	880	133.9	770	114.7

from the PAHO/WHO NCD Country Capacity Survey *(9)*. This is a standardized global survey which was completed June–October, 2015 by the designated Ministry of Health official(s) responsible for the national NCD programme.

Results

Sufficient data were found to include 13 countries/territories from CARICOM in this analysis (Antigua and Barbuda, the Bahamas, Barbados, Belize, Dominica, Grenada, Guyana, Jamaica, St Kitts and Nevis, St Lucia, St Vincent and the Grenadines, Suriname, and Trinidad and Tobago).

Overview of cancer in the Caribbean

The population sizes are highly variable in the countries included in this analysis, ranging from as few as 52,000 people in St Kitts & Nevis, to 2.8 million people in Jamaica. The countries are generally classified as middle income and upper-middle income, with gross national income ranging from US$ 6,940/capita to US $31,970/capita and with national health expenditures from 2.1%–4.7% of GDP (Table 1). Cancer is the second leading cause of death after cardiovascular diseases in all countries included in this analysis, except for Guyana, and generally accounts for approximately 20% of total deaths, with the exception of Guyana and Belize where cancer represents only 8% and 12% of total deaths (Table 1).

The highest cancer mortality rates are observed in St Vincent & the Grenadines and Grenada, while Belize and Guyana have the lowest rates. In most countries, cancer mortality is much higher in males than females, except in the Bahamas, Belize and Guyana where female cancer mortality is higher (Table 1).

Among men, prostate cancer was the leading cause of cancer deaths in all countries. Lung cancer was the second or third leading cause of cancer deaths among men, with the exception of St Kitts and Nevis where it was the fourth ranked cancer

Table 2: **Ranking of the top five causes of cancer death, by sex, in selected countries in the Caribbean region** *(10)*

	Male						Female					
	Prostate	Lung	Colorectal	Stomach	Pancreas	Liver	Breast	Cervix	Colorectal	Uterine corpus	Ovary	Lung
Antigua & Barbuda	1	2	3	-	-	4	1	4	2	5	3	-
Bahamas	1	2	3	4	-	-	1	3	2	-	4	5
Barbados	1	3	2	4	5	-	1	3	2	4	5	-
Belize	1	2	5	4	-	3	2	1	-	3	-	5
Dominica	1	2	5	3	4	-	1	2	3	-	-	5
Grenada	1	2	3	5	-	-	1	2	5	3	4	-
Guyana	1	3	2	4	5	3	1	2	5	3	4	
Jamaica	1	2	3	4	-		1	2	3	4	-	5
St Kitts & Nevis	1	4	3	-	-	2	1	2	5	-	4	-
St Lucia	1	2	4	3	5	-	1	2	3	-	4	-
St Vincent & the Grenadines	1	3	2	4	5	-	1	2	4	3	5	
Suriname	1	2	3	5	-	4	2	1	3		5	4
Trinidad &Tobago	1	2	3	5	4	-	1	2	3	4	5	-

Table 3: **Cancer risk factor prevalence in selected countries in the Caribbean** *(8,11–14)*

Country	Current tobacco smoking prevalence in adults(%)		Alcohol consumption (litre/person/year)		Overweight and obesity in adults (%)		HPV prevalence in women with normal cytology (%)
	male	female	male	female	male	female	
Antigua & Barbuda	n/a	n/a	7.7	3.1	55.4	68.3	n/a
Bahamas	26.9	6.4	10.1	3.9	66.3	71.5	n/a
Barbados	14.2	1.6	9.8	4.0	57.2	67.4	n/a
Belize	17.7	1.4	14.5	2.5	48.5	59.1	10.1
Dominica	16.6	3.3	10.2	4.1	53.5	63.2	n/a
Grenada	30.3	6.5	17.9	7.3	50.6	64.5	n/a
Guyana	29.5	3.2	11.7	4.7	43.9	62.1	11.0
Jamaica	22.1	7.2	7.1	2.8	52.1	65.9	54.0
St Kitts & Nevis	16.2	1.1	11.8	4.7	53.0	64.7	25.2
St Lucia	n/a	n/a	15.1	5.9	51.1	63.4	n/a
St Vincent & the Grenadines	21.9	2.5	9.2	3.9	51.3	61.3	29.6
Suriname	34.0	6.6	9.4	3.9	53.7	63.3	n/a
Trinidad & Tobago	33.5	9.4	9.7	3.9	55.4	67.2	40.6

death in men. Colorectal cancer also ranked as the second or third leading cause of cancer-related deaths in almost all countries, with the exception of Belize, Dominica and St Lucia, where it ranked fourth or fifth. Stomach cancer ranked as the fourth leading cause of cancer deaths in six countries, whereas pancreatic and liver cancer ranked fourth in two countries (Table 2). Oral cancer may be an emerging problem as well in this region, as it ranked among the top five causes of cancer deaths in two of the countries (Antigua & Barbuda, Barbados) and was within the top 10 cancers in the remaining countries.

Among women, breast cancer is the leading cause of cancer deaths in all countries, with the exception of Belize and Suriname where cervical cancer ranked as the leading cause. In the majority of countries, cervical cancer was ranked as the second or third leading cause of cancer deaths, with the exception of three countries (Antigua and Barbuda, the Bahamas and Barbados), where colorectal cancer was ranked second. Uterine corpus and ovarian cancers are among the fourth and fifth leading causes of cancer death, whereas lung cancer ranked within the top five in only five countries.

Cancer risk factors

Prevalence of the main cancer risk factors is summarized in Table 3. Tobacco smoking, perhaps the single most important risk factor, ranges from a high of 21.1% and 20.0% in Trinidad & Tobago and Suriname, respectively, to a low of 7.5% in Barbados among adults (15 years of age and older). Males have a much higher smoking prevalence than females in all countries, and this difference is as low as 3.5 times higher in men than women in Trinidad & Tobago, to more than a tenfold difference in Belize and St Kitts and Nevis (Table 3). Alcohol consumption is variable among countries, with a low of 4.9 litres/person/year in Jamaica, to a high of 12.5 litres/person/year in Grenada. Men consume much

Table 4: **Cancer plans and primary prevention policies in selected Caribbean countries *(9)***

Country	National cancer policy/plan/ strategy	Tobacco Control Policy (PAHO tobacco control report 2016)	Obesity prevention plan	Alcohol reduction plan	Hepatitis B vaccination (year initiated, estimated coverage latest year data available)	HPV vaccination (year initiated, target group)
Antigua and Barbuda	Yes	• FCTC ratified in 2006 • 20% of retail price is tax on cigarettes • smoke-free environments only in government buildings • no health warnings • no bans on advertising	No	No	Yes (1999, 98%)	Yes (2016, boys and girls 9 years of age)
Bahamas	No	• FCTC ratified in 2009 • 43% of retail price is tax on cigarettes • no smoke-free environments • health warnings • no bans on advertising	No	No	Yes (2001, 96%)	Yes (2015, boys and girls 10- 12 years of age)
Barbados	Yes	• FCTC ratified in 2005 • 42% of retail prices is taxes on cigarettes • smoke-free environments • no health warnings • no bans on advertising	Yes (2009)	No	Yes (2000, 87%)	Yes (2014, girls 11-12 years of age)
Belize	Yes	• FCTC ratified in 2005 • 37% of retail price is tax on cigarettes • no smoke-free environments • health warnings • no bans on advertising	in development	in development	Yes (2000,98%)	Yes (2016, girls 10 years of age)
Dominica	Yes	• FCTC ratified in 2006 • 23% of retail price is tax on cigarettes • no smoke-free environments • no health warnings • no bans on advertising	No	No	Yes (2006,74%)	No
Grenada	Yes	• FCTC ratified in 2007 • 48% of retail price is tax on cigarettes • no smoke-free environments • no health warnings • no bans on advertising	No	No	Yes (2000,97%)	No
Guyana	in development	• FCTC ratified in 2005 • 25% of retail price is tax on cigarettes • few smoke-free environments • health warnings • no bans on advertising	In development	In development	Yes (2001,97%)	Yes (2012, girls 10- 13 years of age)
Jamaica	Yes	• FCTC ratified in 2005 • 43% of retail price is tax on cigarettes • smoke-free environments • health warnings • incomplete bans on advertising	In development	In development	Yes (2003,96%)	No
St Kitts & Nevis	Yes	• FCTC ratified in 2011 • 20% of retail price is tax on cigarettes • no smoke-free environments • no health warnings • no bans on advertising	No	No	Yes (1997, 98%)	No
St Lucia	Yes	• FCTC ratified in 2005 • 63% of retail price is tax on cigarettes • no smoke-free environments • no health warnings • no bans on advertising	In development	In development	Yes (2002, 100%)	No
St Vincent & the Grenadines	No	• FCTC ratified in 2010 • 17% of retail price is tax on cigarettes • no smoke-free environments • no health warnings • no bans on advertising	No	No	Yes (xx)	No
Suriname	yes	• FCTC ratified in 2008 • 56% of retail price is tax on cigarettes • smoke-free environments • health warnings • bans on advertising	No	No	Yes (2003,84%)	Yes (2013, girls 9-13 years of age)
Trinidad and Tobago	No	• FCTC ratified in 2004 • 30% of retail price is tax on cigarettes • smoke-free environments • health warnings • bans on advertising	Yes (2012)	No	Yes (2003, 92%)	Yes (2013, girls 11-12 years of age)

more alcohol, at least twice as much or more, than women in all countries.

Overweight/obesity (BMI>25 kg/m^2) is of significant concern, with an average prevalence of 59.4% among adults in this sub-region. Women are much more likely to be overweight or obese than men, ranging from a high of 71.5% of women in the Bahamas and low of 61.3% of women in St Vincent and the Grenadines; as compared to a high of 66.3% of men in the Bahamas and low of 43.9% of men in Guyana.

Infection-related cancers are common in the Caribbean and relevant risk factors include HPV infection (cervical cancer), Hepatitis B or C infection (liver cancer) and H. pylori infection (stomach cancer). HPV prevalence studies have been conducted in the past several years in a few countries in the Caribbean and the prevalence rates are observed to range widely across countries, from 54% in Jamaica to 11% in Guyana (Table 3). No data were found on prevalence of either Hepatitis infection, or H. pylori infection rates in this region.

Cancer plans and policies

Countries have begun to establish national cancer control plans, as a means of defining the strategies, interventions and resources that will be devoted to prevent and control risk factors nationally. All countries in our analysis reported having a national cancer control policy/plan/strategy, with the exception of the Bahamas, St Vincent and the Grenadines and Guyana (although the latter is in development). The World Health Organization Framework Convention on Tobacco Control (FCTC) has been ratified in all countries, beginning with Trinidad & Tobago in 2004 and other countries following suit mainly between 2005–2007, and with St Kitts & Nevis ultimately signing on to this treaty in 2011. The implementation of its measures, notably the six most effective MPOWER measures (monitoring, 100% smoke-free environments, treatment of tobacco dependence, health warnings, ban on advertising, promotion and sponsorship and tobacco taxes/pricing) has not been achieved (Table 4). Policies to reduce harmful use of alcohol are lacking in the Caribbean and obesity prevention plans have not yet been developed in the majority of countries, with the exception of Barbados and Trinidad & Tobago (Table 4).

Hepatitis B vaccination has been fully integrated into national immunization programmes throughout the region, beginning in 1999 and with vaccine coverage exceeding 90% in most countries (Table 4). HPV vaccines, available since 2006, on the other hand, have not yet been fully implemented in this region where seven countries report introduction, beginning in Guyana in 2012, Suriname and Trinidad & Tobago in 2013, and more recently Antigua & Barbuda, Barbados, and the Bahamas. Six countries, predominantly from the Eastern Caribbean, have not yet introduced the HPV vaccine into their national immunization programme. No data on HPV vaccine coverage from the Caribbean were found.

Cancer screening and early detection

Breast cancer screening programmes, mainly opportunistic, have been established in eight countries (Antigua & Barbuda, the Bahamas, Belize, Dominica, Grenada, Guyana, Jamaica, St Lucia, St Vincent and the Grenadines), mainly using clinical breast examination as the modality and with a very wide target population (Table 5). Mammography has not yet been integrated as the main screening modality in this region, with the exception of the Bahamas and Dominica. No information was found on breast cancer screening coverage.

For cervical cancer, almost all countries report having a screening programme, mainly opportunistic, with the exception of Barbados and Suriname which report not having a population-wide screening programme. The traditional Pap test is the most commonly used screening modality in all countries. Belize and Guyana have also introduced VIA screening, and no countries have yet introduced HPV testing, which is a far more effective screening test. No information was found on screening coverage.

Colorectal cancer screening has not yet been initiated in this region, with the exception of Antigua and Barbuda which reports an opportunistic programme using colonoscopy in the general population. Prostate cancer early detection has been initiated in five countries (Antigua & Barbuda, the Bahamas, Belize, Jamaica, St Lucia), but with PSA testing only in Belize and St Lucia.

Cancer treatment capacity

A cancer care system includes colposcopy services and treatment for cervical precancer (cryotherapy, LEEP (loop electrosurgical excision procedure), cold knife conization (CKC)), pathology services, surgery, chemotherapy and radiotherapy and palliative care. Chemotherapy treatment is reported as generally available only in six countries – Antigua & Barbuda, Barbados, Jamaica, Suriname and Trinidad & Tobago; while radiotherapy services are available in only seven countries – Antigua and Barbuda, the Bahamas, Barbados, Guyana, Jamaica, Suriname, Trinidad and Tobago; and cancer surgery in six of these countries (Table 6). Palliative care access, as measured by opioid consumption in morphine equivalence minus methadone, is abysmally low in all countries, well below 10 mg/capita (Table 6). This access is significantly lower than in North America where, for example, it is 733 mg/capita in Canada *(16)*.

Cancer registries, a fundamental aspect of cancer control, capture and provide necessary population data on new cancer

Table 5: **Cancer screening programmes in selected Caribbean countries *(9)***

		Antigua & Barbuda	Bahamas	Barbados	Belize	Dominica	Grenada	Guyana	Jamaica	St Kitts and Nevis	St Lucia	St Vincent & the Grenadines	Suriname	Trinidad & Tobago
Breast cancer	Screening programme	Yes, opportunistic screening	Yes, opportunistic screening	No	Yes, opportunistic screening	Yes, opportunistic screening	Yes opportunistic screening	No	Yes opportunistic screening	No	Yes, organized program	Yes, opportunistic screening	No	No
	Screening method	CBE	Mammography	n/a	CBE	Mammography	Not specified	n/a	CBE	n/a	CBE	CBE	n/a	n/a
	Population targeted by the program	General female population	Not specified	n/a	21-70 years of age	General female population	18 -45 years of age	n/a	General female population	n/a	General female population	18-70 years of age	n/a	n/a
Cervical cancer	Screening programme	Yes, opportunistic screening	Yes, opportunistic screening	No	Yes, organized program	Yes, opportunistic screening	Yes, organized programme	Yes, organized programme	Yes, organized programme	Yes, opportunistic screening	Yes, organized programme	Yes, opportunistic screening	No	Yes, organized program
	Screening method	Pap test	Pap test	n/a	Pap test/ VIA	Pap test	Pap test	VIA test	Pap test	Pap test	Pap test	Pap test	n/a	Pap test
	Population targeted by the programme	General female population	18-59 years of age	n/a	21-70 years of age	18-65 years of age	General female population	30-49 years of age	25-54 years of age	18-55 years of age	General female population	18-60 years of age	n/a	18 years of age +
Prostate cancer	Early detection programme	Yes, opportunistic	Yes, opportunistic	No	Yes, opportunistic	No	No	No	Yes, opportunistic	No	Yes, opportunistic	No	No	No
	Method	Prostate palpation	Prostate palpation	n/a	PSA test	n/a	n/a	n/a	Prostate palpation	n/a	PSA test	n/a	n/a	n/a
	Population targeted by the programme	General male population	Males 40-75 years of age	n/a	Males 50 years and older	n/a	n/a	n/a	Males 40 years and older	n/a	Males 40 years and older	n/a	n/a	n/a
Colorectal cancer	Screening programme	Yes, opportunistic screening	No	No	No	No	No	No	No	No	No	No	No	No
	Screening method	Colonoscopy	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Population targeted by the programme	General adult population	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

cases and deaths. In our analysis, we found only four countries (Barbados, Jamaica, Guyana, and Trinidad & Tobago) with population-based cancer registries that meet international standards of quality and report data in an ongoing and systematic manner.

Civil society initiatives

Across the region other actors, such as civil society organizations (CSOs), academia, regional and international donor agencies, and the private sector, have contributed significantly to the cancer control landscape through prevention, screening and diagnosis, treatment and psychosocial and palliative care. The Healthy Caribbean Coalition (HCC) is one such entity. The HCC is the only regional network of over 100 health and non-health NCD-focused CSOs including 21 national cancer societies which collectively form the Caribbean Cancer Alliance (CCA). National cancer societies play a central role in educating local communities, providing screening and referral and in some instances offering support, counselling and end of life care; especially for vulnerable and marginalized populations, such as the poor, youth and indigenous communities. Through the HCC, and in partnership with the public and private sector, the CCA has focused its efforts on advocacy for expanded cervical cancer screening and increased HPV vaccination coverage. Since 2013, when the HCC and the American Cancer Society hosted a cervical cancer advocacy capacity-building workshop, the CCA has partnered with PAHO to develop a joint cervical cancer situation analysis *(17)*; launched a regional petition to "End Cervical Cancer Now" which received approximately 20,000 signatures *(18)*; successfully lobbied for the introduction of national HPV vaccination programmes in two territories; and contributed to national attainment of cervical cancer screening targets in support of global cervical cancer screening targets found in the existing and updated Appendix III of the WHO Global NCD Action Plan 2013–2020 *(6)*. Most recently, the HCC and the CCA reaffirmed a collective commitment to high-level cancer advocacy through the Caribbean Cancer Advocacy Agenda launched on World Cancer Day 2017 *(19)*. The agenda highlighted priority advocacy areas from the perspective of cancer survivors. In support of the 2030 agenda,

Table 6: **Cancer treatment and palliative care capacity in selected Caribbean countries (*9, 15*)**

	Available in public sector	Not available in public sector
Cervical precancer treatment services available with colposcopy, cryotherapy, LEEP/LEETZ and/or cold-knife conization	Bahamas, Barbados, Belize, Dominica, Jamaica, St Kitts & Nevis, Guyana, Suriname, Trinidad & Tobago	
Pathology services for cancer diagnosis	Antigua and Barbuda, Bahamas, Barbados, Dominica, Grenada, Jamaica, St Kitts and Nevis, St Lucia, Suriname, Trinidad and Tobago	Belize, Guyana, St Vincent & the Grenadines
Cancer surgery	Antigua and Barbuda, Bahamas, Barbados, Jamaica, Suriname, Trinidad and Tobago	Belize, Dominica, Grenada, Guyana St Kitts and Nevis, St Lucia, St Vincent & the Grenadines
Radiotherapy services	Antigua and Barbuda, Bahamas, Barbados, Guyana, Jamaica, Suriname, Trinidad and Tobago	Belize, Dominica, Grenada, St Kitts and Nevis, St Lucia, St Vincent & the Grenadines
Chemotherapy available	Antigua and Barbuda, Bahamas, Barbados, Jamaica, Suriname, Trinidad and Tobago	Belize, Dominica, Grenada, Guyana St Kitts and Nevis, St Lucia, St Vincent & the Grenadines
Palliative care access as measured by opioid consumption (in morphine equivalence minus methadone, mg/capita)	**0-1.9mg/capita:** Grenada, Suriname **2.0-4.9mg/capita:** St Kitts & Nevis, Dominica, Guyana, Jamaica, St Lucia, St Vincent & the Grenadines **5.0-7.9 mg/capita**: Trinidad & Tobago **8.0+ mg/capita:** Barbados	n/a

the 25x25 targets, the recently endorsed Cancer Declaration, and in the lead-up to the 2018 UNHLM, the HCC and the CCA will continue to work in multisectoral partnerships to advocate for cancer policy and programming across the following priority areas: HPV vaccination, cervical cancer screening, improved palliative care; and creating networks to facilitate the establishment and strengthening of affordable and accessible regional treatment platforms.

The HCC has also been among regional catalysts and partners in the Caribbean Cancer Control Leadership Forum (CCCLF), led by the United States National Institutes of Health/National Cancer Institute to support cancer control planning in the region through engagement of multiple sectors, introduction of evidence-based resources and practical planning tools, technical assistance, and information exchange between Caribbean countries. Since its inception in 2015, the CCCLF has worked with teams comprised of government, academic, care delivery, and civil society professionals from eight Caribbean countries, as well as individuals from five additional countries in the region. Outcomes thus far include providing technical guidance for the Bahamas in their successful bid to pass cancer reporting legislation and initiate a national registry and technical support on cervical cancer prevention for Guyana and Suriname as they develop their screening programmes.

Discussion

The cancer mortality rates in the Caribbean countries reviewed in our analysis are comparable to rates observed in other world regions and patterns are similar with leading causes of cancer death from prostate, lung and colorectal cancers in men, and breast and cervix in women *(20)*. However, the remarkable difference is in prostate cancer, where the Caribbean region has been noted to have the highest age-standardized rates in the world *(21)*, and, similar to the experience of African American men, is largely attributed to race and genetic factors *(22)*.

Although an estimated 40% of cancers can be prevented through health promoting policies and behaviour change *(23)*, our analysis highlights the limited cancer prevention policies in place in this sub-region. Of concern are the limited policies and regulations related to healthy eating in the face of a high prevalence of overweight/obesity. Another concern is the limited implementation of HPV vaccines in this sub-region, which is lagging as compared to other world regions *(24)*. This highlights the need for increasing advocacy activities of civil society organizations to garner greater political and public support for stronger tobacco, alcohol, diet and physical activity policies, as well as HPV vaccination.

A comprehensive cancer plan can reduce cancer mortality and improve quality of life *(25)*. While it is encouraging to note that almost all countries have initiated plans, it will require efficient health systems with sufficient financial and human resources to ensure accessible, quality cancer care. Our analysis highlights the limited health system capacity in this

sub-region and investments are clearly needed to increase access to care. An essential package of cancer prevention and control interventions is estimated to cost about 3% of total public spending on health *(26)*, but this may be prohibitive for many countries in this sub-region and innovative funding mechanisms may be the solution. One such example is in pooled procurement mechanisms to increase access, availability, quality and consistent supply of essential cancer drugs. The Organization of Eastern Caribbean States Pharmaceutical Procurement Scheme *(27)* and the PAHO Strategic Fund *(28)* provide such services and are key opportunities to bridge the gaps in access to chemotherapy and opioids. Another example of innovations in cancer care is in the shared cancer treatment services which are emerging through the establishment of informal networks, supported by civil society, linking patients in countries with no cancer treatment services to countries where such services exist.

Nevertheless, there is a need to extend and strengthen regional and national multisectoral partnerships in cancer which facilitate knowledge and resource sharing across and within the countries/territories. This has already begun, with initiatives such as the PAHO Women's Cancer Initiative *(29)*, Healthy Caribbean Coalition Cancer Initiative, Caribbean Cancer Control Leaders Forum, the International Atomic Energy Agency's Program of Action on Cancer Therapy, and the IARC/CARPHA/CDC/NCI Caribbean Cancer Registry Initiative. But these initiatives are nascent and more intensified cooperation, especially for cancer treatment, is needed.

As the global health community prepares to report on progress in NCD prevention and control for the 2018 UN High-Level Meeting on NCDs, the Caribbean sub-region will be well positioned to highlight its advances in cancer control, while describing its urgent need for more intense multisector collaboration, technical assistance and funding support to improve cancer care and reduce the cancer burden. ■

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Sir Trevor Hassell is the President of the Healthy Caribbean Coalition, Chairman of the Barbados National Chronic Non-Communicable Diseases Commission, and Barbados Special Envoy for Chronic Diseases. He is leading the civil society effort in the Caribbean on NCD advocacy, capacity-building and enhancement of communications applying a "whole of society" and multisectoral approach to NCD prevention and control.

References

1. CARICOM. Declaration of Port-of-Spain: Uniting to stop the epidemic of chronic NCDs. Port of Spain, Trinidad, 2007. Accessed on May 4, 2017 from: http://caricom.org/media-center/communications/statements-from-caricom-meetings/declaration-of-port-of-spain-uniting-to-stop-the-epidemic-of-chronic-ncds
2. Samuels TA, Hospedales CJ. From Port-of-Spain summit to United Nations High Level Meeting CARICOM and the global non-communicable disease agenda. *West Indian Med J*. 2011 Jul;60(4):387-91
3. United Nations. Political Declaration of the High-level Meeting on the Prevention and Control of Noncommunicable Diseases. New York City: UN, 2011. Accessed May 4, 2017 from: http://www.un.org/en/ga/ncdmeeting2011/
4. World Health Organization. Global action plan for the prevention and control of noncommunicable diseases. Geneva: WHO, 2013. Accessed May 4, 2017 from: http://apps.who.int/iris/bitstream/10665/94384/1/9789241506236_eng.pdf
5. Pan American Health Organization. Plan of Action for the Prevention and Control of NDCs in the Americas 2013-2019. Washington, DC : PAHO, 2014. Accessed May 4, 2017 from: http://www.paho.org/hq/index.php?option=com_content&view=article&id=11275%3Aplan-action-ncds-americas-2013-2019&catid=7587%3Ageneral&Itemid=41590&lang=en
6. World Health Organization. Preparation for the third High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases, to be held in 2018. [internet] Accessed May 26 2017 from: http://apps.who.int/iris/bitstream/10665/94384/1/9789241506236_eng.pdf
7. World Health Organization. Cancer prevention and control in the context of an integrated approach. [internet] Accessed May 26, 2017 from: http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_32-en.pdf
8. Pan American Health Organization. PLISA/Health Information Platform for the Americas.[internet] Accessed May 24, 2017 from: http://www.paho.org/data/index.php/en/indicators-mortality.html
9. Pan American Health Organization. Profile of capacity and response to noncommunicable diseases and their risk factors in the Region of the Americas. Country capacity survey results, 2015. PAHO, Washington, DC. 2017. Accessed June 10, 2017 from: http://iris.paho.org/xmlui/handle/123456789/34096
10. Razzaghi H, Quesnel-Crooks S, Sherman R, et al. Leading Causes of Cancer Mortality — Caribbean Region, 2003–2013. *MMWR Morb Mortal Wkly Rep* 2016;65:1395–1400
11. Pan American Health Organization. Tobacco Control Report for the Region of the Americas. WHO Framework Convention on Tobacco Control: 10 Years Later. Washington, DC: PAHO, 2016. Accessed May 4, 2017: http://www.paho.org/hq/index.php?option=com_content&view=article&id=11965&Itemid=40312&lang=en
12. Hosein F, Mohammed W, Zubach V, Legall G, Severini,A. Human papillomavirus genotypes in invasive cervical squamous cell carcinoma in Trinidad. *Rev Panam Salud Publica.* 2013;33(4):267-70
13. Andall-Brereton GM, Hosein F, Salas,R.A, Mohammed,W, Monteil M.A, Goleski V, Severini,A, Quesnel,S.M.; Carrington,C.V.; Boodram,L.L.; Boisson,E.; Akpaka,P.E.; Paul,R.C. Human papillomavirus genotypes and their prevalence in a cohort of women in Trinidad. *Rev Panam Salud Publica.* 2011;29(4):220-6.
14. Lewis-Bell K, Luciani S, UngerER, Hariri S, McFarlane S, Steinau M, Prieto-Lara E, Vicari AS, Irons B, Lewis MJ, Andrus JK. Genital human papillomaviruses among women of reproductive age in Jamaica. *Rev Panam Salud Publica.* 2013;33(3):159-65
15. University of Wisconsin Pain and Policy Study Group. Opioid Consumption Database. [internet] Accessed June 10, 2017 from: http://www.painpolicy.wisc.edu/countryprofiles
16. International Narcotics Control Board. Report of the International Narcotics Control Board for 2016. United Nations: INCB, Vienna, Austria, 2017. Accessed May 14, 2017 from: http://www.incb.org/documents/Publications/AnnualReports/AR2016/English/AR2016_E_ebook.pdf
17. Pan American Health Organization/Healthy Caribbean Coalition. Situational Analysis of Cervical Cancer Prevention and Control in the Caribbean. Washington, DC: PAHO, 2013. Accessed June 16, 2017 from https://www.healthycaribbean.org/wp-content/uploads/2016/11/Carribean-cxca-situation-analysis-2013.pdf
18. Healthy Caribbean Coalition. Caribbean Cervical Cancer E-Petition Data Infographic. 2017. [internet] Accessed June 14, 2017 from: https://www.healthycaribbean.org/cccep-data-infographic/
19. Healthy Caribbean Coalition. Caribbean Cancer Advocacy Agenda. 2017. [internet] Accessed June 14, 2017 from: https://www.healthycaribbean.org/wp-content/uploads/2017/02/Caribbean-Cancer-Advocacy-Agenda.pdf
20. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* 2015 Mar 1;136(5):E359-86
21. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global Cancer Statistics. *CA Cancer J Clin.* 2011 Mar-Apr;61(2):69-90
22. Odedina FT, Akinremi TO, Chinegwundoh F, Roberts R, Yu D, Reams RR, Freedman ML, Rivers B, Green BL, Kumar N. Prostate cancer disparities in Black men of African descent: a comparative literature review of prostate cancer burden among Black men in the United States, Caribbean, United Kingdom, and West Africa. *Infectious Agents and Cancer.* 2009;4(Sl):1-8
23. World Health Organization. Cancer control: Prevention. *WHO guide for effective programmes.* Geneva:WHO, 2007
24. Brotherton JML, Bloem PJN. HPV Vaccination: Current Global Status. *Curr Obstet Gynecol Rep.* 2015;4:220-233
25. World Health Organization. National cancer control programmes. *Policies and managerial guideline.* Geneva:WHO, 2002
26. Gelband H, Sankaranarayanan R, Gauvreau CL, Horton S, Anderson BO, Bray F, Cleary J, Dare AJ, Denny L, Gospodarowicz MK, et al. Costs, affordability, and feasibility of an essential package of cancer control interventions in low-income and middle-income countries: key messages from Disease Control Priorities, 3rd edition. *Lancet.* 2016 May 21;387(10033):2133-44
27. Organization of Eastern Caribbean States. Pharmaceutical Procurement Scheme [internet]. Accessed June 14, 2017 from: http://www.oecs.org/topics/pharmaceuticals
28. Pan American Health Organization. PAHO Strategic Fund. [internet] Accessed June 14, 2017 from: http://www.paho.org/hq/index.php?option=com_content&view=article&id=12163&Itemid=42005
29. Pan American Health Organization. Women's Cancers in the English Caribbean: A regional multi-sector discussion to define feasible strategies to improve the effectiveness of breast and cervical cancer programs. Washington, DC: PAHO, 2016. Accessed June 14, 2017 from: http://www.paho.org/hq/index.php?option=com_content&view=article&id=11948%3Aforum-womens-cancer-in-the-english-caribbean-miami-11-12-may-2016&catid=3788%3Acancer-events&Itemid=41954&lang=en

CANCER IN THE COMMONWEALTH

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The Commonwealth's community of nations provides a unique opportunity for collaboration in research and training between high-income, technologically advanced countries and the middle- and low-income countries that are set to bear a disproportionate share of its cancer burden. Evidence-based practice would be strengthened by more accurate cancer registration and scientific research synthesis. The challenge facing its leadership is how to inspire the timely development of resources by the governments of its Member States.

The Commonwealth is a voluntary association of governments. With a combined head count of 2.3 billion, its 52 Member States represent nearly a third of the global population and over a quarter of the counties of the world *(1)*. In terms of healthcare, the heterogeneity of this unique grouping is more significant than its magnitude. The Commonwealth includes countries in every continent and hemisphere, in widely varying geophysical environments, with societies of differing sociocultural norms, demographic profiles and levels of political and economic development. In July 2017, the World Bank classified 14 Commonwealth Member States as high-income countries (HIC) with an annual gross national income (GNI) per capita of US$ 12,236 or more; 17 as upper middle-income countries (UMI) with a GNI per capita between US$ 3,956 and US$ 12,235; 15 as lower middle-income countries (LMI) with a GNI per capita between US$ 1,006 and US$ 3,955; and six as low-income counties (LIC) with a GNI per capita of US$ 1,005 or less *(2)*.

Cancer registration

Governments require reliable evidence in order to make informed decisions *(3)*. Regrettably, Commonwealth cancer registry data remains incomplete and of variable quality. The International Agency for Research on Cancer's (IARC) Globocan 2012 database does not include data on 11 of the 52 Commonwealth Member States (Antigua and Barbuda, Dominica, Grenada, Kiribati, Nauru, Saint Lucia, St Kitts and St Nevis, St Vincent and The Grenadines, Seychelles, Tonga, and Tuvalu); smaller countries that have an estimated combined population of 924,874 (2015) *(4)*. Some of the data from the 41 Commonwealth countries that are presented in Globocan may be based on regional estimates. The data from only six of the 40 Commonwealth Member States (Australia, Canada, Malta, New Zealand, Singapore and the United Kingdom) represented in Globocan 2012 are accorded the highest "A-1-1-1" score by IARC for the availability of incidence and mortality data at the country level *(5)*.

With these caveats, Globocan data indicates that in 2012 the 41 Commonwealth Member States it reports on had 2,423,557 new cases of cancer and 1,479,496 deaths from cancer *(6)*. Looking forward to 2035, cancer incidence in these 41 countries is predicted to rise by 78% to 4,312871 new cases per annum and cancer mortality by 83% to 2,696,496 deaths per annum. These increases are significantly higher than the predicted increases in global incidence of 70% (14,067,894 (2012) to 23,980,858 (2035)) and 78% in global mortality (8,201,575 (2012) to 14,634,144 (2035)) *(6)*.

These predicted increases in cancer burden will not be uniform across the board. Whereas in high-income Commonwealth Member States, such as the United Kingdom and Canada, the estimated number of new cases is expected to rise by 37% and 59% respectively (UK: from 327,812 (2012) to 449, 508 (2035); Canada: from 182,182 (2012) to 290,565 (2035)). Less wealthy Member States, such as Malawi and Papua New Guinea will see their cancer incidence double in size over the same period (Malawi: from 15,349 (2012) to 30,980 (2035); Papua New Guinea: from 7,365 (2012) to 14,719 (2035)) *(6)*.

Cervical cancer

Cervical cancer is the most easily preventable cancer through HPV vaccination and community screening. In 2012 Commonwealth countries carried a 40% share (208,807 new cases) of global cervical cancer incidence and 43% of global cervical cancer mortality (115,275 deaths) and over half a million women were living with cervical cancer in the Commonwealth (5-year prevalence: 542,090). Globocan data estimates that within the Commonwealth cervical cancer is the leading female cancer in 13 Member States, the second-most common in 18 Member States, and the leading, or second-

highest cause of death from cancer, in females in 29 Member States.

There is a strong association between Gross National Income (GNI) and cervical cancer. Of the 31 Commonwealth Member States where Globocan estimates cervical cancer is either the leading or the second-most common female cancer, only three (The Bahamas, Brunei Darussalam and Trinidad and Tobago) are classified as high-income countries by the World Bank. The same pattern applies to mortality. Of the 29 Commonwealth Member States where cervical cancer is either the leading or the second-most common cause of female cancer deaths, only one is a high-income economy (Trinidad and Tobago). The six Commonwealth Member States with the highest number of cervical cancer cases and deaths are India, Nigeria, Bangladesh, South Africa, Tanzania and Mozambique.

The percentage increase in new cases of cervical cancer within the Commonwealth during the period 2012–2035 is predicted to be 66% (208,788 to 347,645) which far exceeds the estimated global increase of 43% (527,624 to 756,273 new cases). Similarly, Commonwealth deaths from cervical cancer will rise by 75% (114,875 to 201,568 deaths) over the same period; this is much higher than the global percentage increase of 56% (265,672 to 416,061 deaths) predicted by IARC

Scientific research

Increasingly, policy-makers and parliamentarians are requiring evidence of the effectiveness of interventions presented in primary or secondary research *(2)*. Commonwealth countries make a major contribution to the published literature on cancer control in low- and middle-income countries (LMIC). An electronic search conducted by INCTR UK of four bibliographic databases (Pubmed, Embase, African Journals Online and WHO's African Index Medicus) for evidence published between 2000 and 2016 relevant to cervical cancer and other HPV-linked cancers in sub-Saharan Africa identified 1,656 reports of research. Of these, 1,414 (85%) reports related to populations or patients in African Commonwealth Member States. Many of the reports of the cancer control research conducted in LMICs lie scattered across the biomedical literature in different databases, conference proceedings and university archives *(7)*. Difficulty in accessing the results of research can lead to missed opportunities to build on proven strategies, or to wasteful duplication of effort. INCTR's search identified 134 reports (101 full articles and 33 conference proceedings) concerning the level of public and professional knowledge/awareness/attitudes/behaviour/ practice (KAABP) surrounding HPV and cervical cancer in Nigeria. This tall pile of papers represents a substantial amount of evidence that deserves to be systematically reviewed and the results considered by policy-makers and research commissioners.

Economic growth and urbanization

Although 38 Commonwealth countries are classified as low- and middle-income countries, the combined gross domestic product of Commonwealth Member States is estimated at US$ 10.4 trillion in 2017 and predicted to reach US$ 13 trillion in 2020. Commonwealth membership has advantages: bilateral costs for trading partners in Commonwealth countries are on average 19% less than between those in non-member countries. Half of the top 20 global emerging cities are in the Commonwealth: New Delhi, Mumbai, Nairobi, Kuala Lumpur, Bangalore, Johannesburg, Kolkata, Cape Town, Chennai and Dhaka *(8)*. Urbanization and overcrowding inevitably increases population exposure to the known risk factors for cancer and other NCDs: poor diet, excessive alcohol consumption, less exercise, increased exposure to manufactured tobacco products. It is these cities, and cities like these, that will fuel the coming wave of cancer incidence in sub-Saharan Africa, India and South East Asia. For as long as labour remains a factor of production or service provision, the health of the national workforce will remain integral to the development of successful economies. The steadily rising incidence of cancers in Commonwealth Member States is already a cause for concern. It deserves attention as an important health and economic problem that needs to be controlled, and this is a job for government. The identification and implementation of innovative cost-effective strategies to prevent and reduce cervical cancers, in particular, will benefit all Commonwealth Member States by highlighting women's health issues and reproductive health, reducing family poverty, and helping Member States with their target of controlling non-communicable diseases in their countries *(9)*.

What is to be done?

Due to its size and composition the Commonwealth enjoys several advantages that make it uniquely suitable for research into the causes and various approaches to the control of cancers *(10)*. Healthcare interventions that test successfully across the diversity of the Commonwealth Member States offer gains for the global economy, as well as a benefit to individual cancer patients and their families. The decision taken by the Commonwealth Health Ministers in Geneva on 21 May 2017 that the theme for their 2018 Meeting should be "*Enhancing the global fight against NCDs; raising awareness, mobilizing resources and ensuring accessibility to universal coverage*" provides a timely opportunity to explore novel strategies for collaboration.

A Commonwealth economic committee for cancer control should be formed in order to take maximum advantage of the heterogeneity of differences in national cancer patterns and economic development. The establishment of a Commonwealth Cancer Fund with a sliding scale of contributions, ranging

from US$ 100,000 from the high-income member states to US$ 25,000 from the low-income countries, would amass an annual pot of over US$ 3 million that could be used to leverage additional funding and resources from non-State actors. By this method modest contributions can build up capacity in cancer control in the smaller and less economically advantaged Member States through skills training and multilateral aid.

Cancers can be very costly to treat. Ministers and parliamentarians have a right to expect good-quality evidence when considering their nation's cancer burden and not to have to rely upon incomplete or regional estimates. Every Commonwealth Member State should have a well-functioning population-based cancer registry reporting data that broadly represents its population, in order to inform public investment decisions in cancer prevention and control, and to assist its government in keeping up its national commitments as part of the Global NCD initiative agreed at the UN High Level meeting in 2011. To this end, given the large number of the world's nations belonging to the Commonwealth, it would be helpful for IARC to introduce the classification "Commonwealth Member State" to its Globocan matrix so that estimates of cancer incidence, prevalence and mortality in these countries can more easily be compared with regional and global estimates.

Whereas the scientific research evidence from high-income countries are relatively easy to retrieve, the Commonwealth Secretariat could make a major contribution by working with in-country experts and non-State actors to facilitate the identification of existing reports of research conducted in, or relevant to, the populations of its low- and middle-income Members States, and make them more easily accessible to policy-makers through the Commonwealth's own information hub.

Despite the launch of the Commonwealth Charter in 2013 and the adoption of the UN's Sustainable Development Goals, poverty remains pervasive in many Commonwealth countries *(11)*. The increases in cervical cancer incidence and mortality facing the Commonwealth will be disproportionate, with the poorest Member States experiencing a doubling of new cases and deaths compared to increases of 22% in total incidence and 44% in total mortality in the high-income Commonwealth Member States *(6)*. The challenge facing all the Commonwealth Member States is the timely development of a level of resources that can match the predicted increase in their individual burdens of disease. Commonwealth Member States should show a sense of urgency in addressing cervical cancer and not be satisfied with achieving the global goals that have been developed under the UN Global NCD initiative.

Forewarned should mean forearmed and the Commonwealth is a voluntary association of governments, not of peoples. The time has come for Commonwealth governments to summon the collective political will to call for a Cancer Summit to explore whether this challenge can be addressed in partnership with, or with the assistance of, other Commonwealth Member States. ■

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References

1. The Commonwealth Secretariat Thecommonwealth.org/about-us
2. World Bank Country Classification July 2017 https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups]
3. Supporting evidence use in African parliaments – Emerging insights. Meeting London 24 April 2017 *Commonwealth Parliamentary Association* 2017
4. The World Fact Book https://cia.gov/library/publications/the-world-factbook
5. GLOBOCAN Data Sources and Methods http://globocan.iarc.fr
6. GLOBOCAN 2012 International Agency for Research into Cancer http://globoca. Iarc.fr
7. Lodge M Ignorance is not strength. *Cancer Control 2013* pp
8. The Commonwealth Secretariat http://thecommonwealth.org/fastfacts
9. Magrath I, Lodge M. *Cancer in the Commonwealth Commonwealth Health Ministers Update 2011* pp19-22
10. Weller D et al Open letter to Baroness Scotland *Lancet Oncology* 2018 vol 18 April e194
11. Taylor P. Poverty: A truly pan-Commonwealth problem. The Royal Commonwealth Society https://www.thercs.org/blogsnews-and-blognews-and-blog/news-and-blog/defining-poverty-across-the-commonwealth/ 2016

PAEDIATRIC CANCER

CHILDHOOD CANCERS IN LOW- AND MIDDLE-INCOME COUNTRIES: PREVENTION AND POTENTIALLY CURABLE TREATMENT?

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Survival disparity for childhood cancers world wide must be reduced. Infection related malignancies offer the possibility of both prevention and affordable treatment. Burkitt Lymphoma, the most common tumour seen in sub-Saharan Africa can be reduced by improving malaria control and cured in at least 60% of cases by short course affordable drugs. HIV/AIDS control has reduced Kaposi Sarcoma incidence. Greater collaboration between those working in communicable and noncommunicable diseases would benefit all children.

Incidence and prevalence

Survival for children with cancer has increased considerably from under 20% in 1970 to 75–80% in 2017 in high-income countries (HICs) *(1)*. This has resulted from the ability to reduce delays in diagnosis, more accurately diagnose specific tumours and from progressive improvement in treatment. There are still challenges with some high risk tumours *(2)*. However the biggest challenge is that only 20% of children worldwide are benefitting from this progress. Eighty-percent of young people live in low- and-middle income countries (LMICs) where survival rates are currently only 10% in LICs and 30% in most MICs *(3, 4)* with clearly some geographical variation. Inaccuracies do arise where there are no population-based registers of incidence and even fewer of mortality. It is calculated that worldwide between 80 and 100,000 young people die unnecessarily from cancer each year because of a failure of diagnosis, and no or inadequate treatment. However recent evidence has shown a 13% increase in worldwide incidence of cancer in young people aged 0–14 years between the decade 1981–1990 and 2001–2010 *(5)*. The increase in part does relate to increased rates of earlier and more accurate diagnoses and the ability to treat especially in middle-income countries and the reduction of under 5-year deaths in LMICs. Such a trend occurred in higher income countries from the 1950s onwards as general health improved and there was a reduction of mortality from infectious diseases. There is compelling evidence that this trend will continue to increase year on year, albeit with some changes in tumour types seen, as societies and economies in each country begin to change *(5)*.

The International Agency for Research on Cancer (IARC) have recently reported, using data from high-quality, high ascertainment population-based cancer registries on 385,509 incident cancers of children and young adults (0–19 Years) occurring over 2.64 billion person-years *(5)*. The calculated overall incidence rates for those aged 0–14 are now 141 per million and for those aged 15–19, 185/ million *(5)*. It is estimated that worldwide there are at least 215,000 new cases per year of children aged 0–14 years with cancer and 85,000 in the age range 15–19 years *(5, 6)*. These figures may well be an under-estimate because of a paucity of reliable cancer registration in many LMICS. In twinning partnerships where assistance from established paediatric oncology units in high-income countries have helped the developing hospital to register all cases they see in the country's hospitals, there is evidence that only 25–33% of cases expected, based on International childhood cancer rates, are actually being diagnosed and treated *(7)*.

The challenges

This gross disparity is due to a number of factors *(7, 8, 9, 10, 11)*:

- Missed or late diagnoses due to lack of public and health professional awareness of cancer signs and symptoms.
- Lack of diagnostic capability, resources and trained laboratory and radiological staff.
- Paucity of trained nurses and doctors to treat patients plus failure to retain those trained within LMICs.
- Overall inadequate facilities and resources in hospitals.
- High rates of co-morbidities (e.g malaria, HIV, TB,

diarrhoea and malnutrition).

- Lack of availability, accessibility and affordability of good quality Essential Medicines (all on WHO listing).
- High rates of treatment refusal and subsequent abandonment most frequently due to non-affordability and/or perception of incurability (9, 12, 13, 14).
- Overwhelming other society issues including natural and man-made crises.

Poverty

In most LMICs families have to bear the total or at least some of the cancer cost burden including for medicines *(7, 9, 14, 15, 16, 17, 18)*. Individual family, community and Governmental poverty all hinder the development of health services but worse than that, it fails each child who is ill but could be cured if resources were available. Considerable assistance has helped in at least 50 countries through a variety of twinning projects linking established paediatric cancer centres in HICs and those who are striving to develop such units in LMICs *(7, 9, 11)*. This can only be a short- to medium-term solution and not sustainable in the longer term. Ultimately, each country will need to resolve the challenges and finance the care of all patients but universal health coverage is a long-term project. However right now at least 50% of childhood cancers can be cured using relatively cheap generic drugs provided the malignancy is diagnosed early before there is significant tumour dissemination.

Prevention

Where resources and finances are limited then it is important to determine what is potentially a "good buy" for families, the country and each Government *(18, 19)*. This makes an initial focus on treatment of infection-related cancers worthwhile because they all have a communicable disease connection in situations where considerable financial input to reduce infections has already been invested over the last two decades (20) as a result of a worldwide initiative. In many LMICs this has led to reduction in malaria, diarrhoea, pneumonia, malnutrition and those with HIV/AIDS have had their chance of long-term survival greatly improved by antiretroviral agents. All the actions taken for communicable diseases over the last 15 years are also having an impact on the incidence of some childhood cancers.

Prevention is always better than having to treat any cancer. Endemic Burkitt Lymphoma *(21, 22, 23)* arises in sub-Saharan Africa, from a combination of high prevalence rates of Plasmodium falciparum malaria, which produces a degree of T-cell immunosuppression resulting in B-Cell proliferation within which the omnipresent Epstein-Barr Virus also proliferate. Ninety-five percent of Endemic BL cases have high levels of EBV Antibodies implying that infection with the virus preceded the development of the tumour. The proliferating cells appear to be transformed by the virus during the immunosuppression induced by malaria episodes. Other potential co-factors may include arboviruses, endemic plant promotors and malnutrition *(24)*. EBV loads appear to increase with attacks of malaria *(25)*. BL accounts for more than 50% of childhood cancers in many sub-Saharan African countries with a peak age of 6–8 years which suggests that an early age EBV sero-conversion is associated with the high incidence of BL *(26)*.

Furthermore, there is a reported 15-fold increase of BL in those who have acquired immunodeficiency syndrome (HIV/AIDS) *(27, 28)*. Consequently, there is increasing evidence that where strenuous efforts have been made to reduce the risk of malaria (mosquito nets/clearance of stagnant water, etc) and the increased dispensing of antiretrovirals that the incidence of BL and other HIV-related tumours have decreased in some regions *(29)*. Of course, the production of an effective anti-malaria vaccine would not only reduce incidence of recurrent malaria in children and particularly cerebral malaria with its high mortality rate but it would also reduce incidence of BL.

Kaposi Sarcoma caused by Human Herpes Virus-8 (HHV-8) is also endemic in sub-Saharan Africa *(30)* but it has shown a significant fall in incidence following use of ART and reduction of immunosuppression where both HIV and HHV-8 are endemic *(31)*.

Liver cancer accounts for 9% of cancer deaths worldwide with 85% occurring in LMICs especially in Asia. Hepato-cellular carcinoma is linked to hepatitis B and C infection. Although hepatic tumours are relatively rare in children there is increasing evidence that national infant HBV vaccination programmes might reduce liver tumour cancer incidence in children and in adults later in life. In both Taiwan and Gambia large scale infant HBV vaccination programmes started 20 years ago are now confirming a reduction of liver tumour incidence *(32, 33, 34)*.

Prevention is generally rare in childhood cancer but for Burkitt lymphoma, Kaposi Sarcoma, liver tumours and all HIV associated tumours there is hope of preventing tumour formation, provided measures (control of known infections, and/or vaccinations) are applied nationally and persistently. If there is any break in control of infections the tumour incidence will increase once again. As described elsewhere in this journal universal HPV vaccination for pre-adolescent boys and girls would not only reduce the risk of cervical cancer in adults but also potentially other HPV-related malignancies.

Avoiding delays in diagnosis *(35,36,37)*

If we cannot prevent malignancies it is always preferable

to recognize the signs and symptoms of potential cancers/leukaemia and diagnose them before there has been significant tumour secondary spread. Diagnostic delays necessitate more intensive therapy to control the malignancy, an increase in the economic burden on those paying for treatment (most commonly families in low-income countries) and considerably more anxiety for patients and families *(8, 9)*. BL classically presents with large abdominal masses, periorbital/mandibular/maxillary swelling, with or without bone marrow and CNS disease. The signs and symptoms of BL are very characteristic and should never be mistaken for anything but tumours. Luckily this tumour is highly sensitive to cyclophosphamide, methotrexate and vincristine, some of the oldest known cytotoxic drugs. Survival is at least 50% for all stages except those with bulky abdominal disease and in some but not all studies CNS or bone marrow (BM) involvement. Hence the importance of early recognition and treatment. It is clear that with adequate and appropriate treatment both CNS and BM disease can be controlled.

The use of poster campaigns targeted at healthcare workers in local clinics, schools, and wherever families meet can be effective provided the messages are clear and repetitive *(38)*. There does remain a degree of stigma associated with cancer in many societies so late presentation still happens, hence the need not only for local health workers to be trained to identify cancer signs but also to overcome the perception by many families that cancer is not curable in children. The use of all forms of media to complement such awareness campaigns are crucial for success in education of the population and professionals have also been found to be very useful. Parent groups of children with cancer and those survivors of cancer can assist immensely in such awareness campaigns and reinforce the potential for curability.

Treatment

At least 50% of childhood cancers can be cured using basic protocols designed and proven over the last 3–4 decades in HICs which can be applied in a graduated intensity process depending on what each hospital and country can manage *(39)*. There are a series of such guidance protocols produced by expert teams from the International Society of Paediatric Oncology (SIOP) covering most of the commonest tumours seen worldwide including the critical need for supportive care guidelines *(40, 41, 42, 43, 44)* and baseline standards for nursing care *(45)*.

Burkitt Lymphoma in 90% of cases can be cured using intensive chemotherapy which is not yet tolerable in most LMICs *(46)* but from evidence accrued in Cameroon and Malawi *(47, 41)* a stratified regimen (based on stage and response to induction) using induction with just cyclophosphamide (iv or oral on days 1, 8, 15) and intrathecal methotrexate + hydrocortisone (Days 1, 8, 15) and followed by consolidation based on the risk grouping by one or two more doses of cyclophosphamide for risk groups 1 and 2 respectively. Only advanced stage disease (Risk group 3) received three doses plus the addition of vincristine. In the Cameroon study *(47)* overall survival with this strategy was 61% at 1 year (100% Stage 1, 85% Stage 2, 60% stage 3, but only 27% stage 4) emphasizing the need for early recognition of the tumour. Such therapy is affordable (for low stages at just US$ 50 for the drugs), short in duration and very tolerable. The International Network for Cancer Treatment and Research, INCTR 03-06 protocol, used in four tertiary equatorial African centres increased survival from an historic 10–20% to 67% for those treated with a three drug initial programme using cyclophosphamide, methotrexate, vincristine and intrathecal therapy for those who went into remission and 62% for those who failed to remit or relapsed early treated with a salvage therapy using ifosfamide, etoposide and cytarabine. This study clearly showed the impact for survival of abdominal disease *(48)*.

There are similar guidelines for Kaposi Sarcoma *(42)*, Retinoblastoma (44) and Wilms Tumour *(43)* all of which are potentially curable, using such standard therapy provided they can be afforded in low-income settings.

Cost of treatment

In most low-middle income countries families carry most or at least some of the financial burden of their child's cancer treatment and care *(19)* but there are only a few studies to date specifically looking at these out of pocket costs *(15, 16, 17, 18)*. Islam et al *(15)* identified in the largest childhood cancer centre in Bangladesh that the basic costs to parents of treating their child with acute lymphoblastic leukaemia was US$ 4,445 with a range from US$ 3,234 to US$ 7,672 depending on how many infectious episodes the patient had during treatment (mean of three serious episodes). These sums are considerably lower than reported from those in HICs *(49)* but still not affordable when 84% of the families in the Bangladeshi unit at the time of the study were living on between 71 and 285 US$ per month. The breakdown of costs there showed that 48.6% was for the purchase of essential medicines all of which are on the WHO Essential Medicines Listing reviewed every two years *(50)* and 26% for transport to and from hospital, food and accommodation for parents whilst the child was in hospital. Investigations, blood products and general treatment costs accounted for the remainder. All medical consultations were free and there were no bed fees.

However, affordability of the essential medicines is just one of the challenges facing patients/families and those caring for children with cancer in LMICs especially, but increasingly

in all countries. There is an increasing crisis in accessibility, availability, quality and affordability of WHO recommended essential medicines for children with cancer *(51, 52, 53, 54)*. They are all off patent, generic drugs more commonly now acquired from generic pharmaceutical companies in a variety of countries but most frequently from India and China. There are problems of adequate and consistent world-wide drug production and distribution, very variable importation processes, considerable variation in drug costs and efficacy of products with inadequate quality control *(52, 53, 55, 55)*. There needs to be a collective collaboration worldwide with all stakeholders working to overcome these challenges and to ensure all that children with cancer can get a fair deal and a real chance of survival.

Incidence and mortality data/registration

The IARC report on Incidence of childhood cancer 2001–10 *(5)* was a major exercise and very informative about overall numbers, and variations in incidence and the reason for them between countries and continents and identified a 13% upward trend in incidence worldwide since the report covering 1981–1990. But it also highlighted the need for much more consistent universal population-based cancer registration. Of 532 invited registries just 153, albeit from 62 countries, met quality standards for the entire decade and could be included in the analyses. The standards used were to ensure that all the basic information about each patient and their diagnosis were as accurate as possible. When reviewing the data from an initial 532 registries worldwide the following standards were applied by a rigorous peer-review process. The numbers of cases confirmed by tumour tissue examination by microscope, and classified according to international grouping (ICCC–3),the proportion only identified by death certification, exclusion of tumours with unlikely site and morphology or unlikely age and tumour without tissue , if more than > 0.05% were rare tumours, overall absolute and relative incidences , proportions of cases and incidence by sex, age, tumour type and stability or not over time and consistency of population data. These are stringent standards by necessity but they are what each hospital register would hope to collect. Clearly since only 153 registries did tick all the boxes for the whole decade there is some way to go before all registries can conform.

What all involved in cancer care, health services and Governments need to recognize is that you cannot develop appropriate services for cancer or any diseases if you do not know how many cases there are to be diagnosed and treated. What happened in higher-income countries was that those treating children with cancer and leukaemias started to develop hospital-based registries collecting most of the data required by the IARC study and these did lead to linking up between hospitals regarding such data inevitably leading to national registration. This took some years to create in some countries but development was quicker in some European countries.

One of the greatest challenges is the paucity of trained pathologists in many LMICs. Many of the international twinning programmes assist by providing in the modern era remote telepathology review systems as interim measures before the local services can be developed *(7,9)*.

Conclusions

Childhood cancer is potentially a "best buy" for health planners in each country with higher cure rates than adult cancers, and a relatively more manageable incidence rate. In each country planners and medics/nurses need to carefully monitor and record every case, plus their outcome. They need to raise awareness of cancer signs and symptoms amongst the public and health workers to reduce missed or late diagnoses. They must try to create the essential supportive care resources and facilities before starting to treat patients. Using the concept of graduated intensity treatment appropriate to their setting they can start to use therapy which can give chance of cure and escalate treatment if that is possible in due course. This is how the successes in HICs was obtained over several decades.

Endemic cancers especially Burkitt Lymphoma, Kaposi Sarcoma, HIV-related tumours and Hepatic tumours are highly likely to be reduced by control of malaria, HIV/AIDS, and vaccination respectively. Those working in oncology and communicable diseases need to join forces to recognize and collaborate more actively. ■

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References

1. McGregor LM, Metzger ML, Sanders R, Santana V M. Pediatric cancers in the new millennium: dramatic progress, new challenges. Oncology 2007; 21(7):809-820
2. Pritchard-Jones K, Pieters R, Reaman GH, Hjorth L, Downie P, Calaminus G et al Sustaining innovation and improvement in the treatment of childhood cancer :lessons from high income countries. *The Lancet Oncology* 2013; http//dx.doi.org/10.1016/s1470-2045 (13)70010-x
3. Pritchard-Jones K, Sullivan R. Children with cancer: driving the global agenda. *The Lancet Oncology* 2013; 14(March):189-191
4. Magrath I, Steliarova-Foucher E, Epelman S, Ribeiro R C, Harif M, Li C-K et al, Pediatric cancer in low income and middle–income countries. *The Lancet Oncology* 2013;10.1016. s1470-2045(13)700008-1
5. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, et al. International incidence of childhood cancer,2001-2010: a population –based registry study. *The Lancet Oncology* 2017;April11th: http://dx.doi.org/10.1016/s1470-2045(17)30186-9
6. International Agency for Research on Cancer-International Childhood Cancer Day (2016). "Much remains to be done to fight childhood cancer" IARC Press release number 241-15 February 2016
7. Hopkins J, Burns E, Eden T. International twinning partnerships: An effective method of improving diagnosis, treatment and care for children with cancer in low-middle income-countries. *Journal of Cancer Policy* http://dx.doi.org/10.1016/j.jcpo2013
8. Ribeiro RC, Steliarova-Foucher E, Magrath I, Lemerle J, Eden T, Forget C, et al. Baseline status of paediatric oncology care in ten low-income or middle-income countries receiving "My Child Matters" support: a descriptive study. *The Lancet Oncology* 2008;9(August 8):721-9
9. Ribeiro RC, Pui CH. Saving the children – Improving childhood cancer treatment in developing- countries. *New England Journal of Medicine.* 2005; 352(21):2158-2160
10. Israels T, Ribeiro RC, Molyneux EM. Strategies to improve care for children with cancer in Sub-Saharan Africa. *European Journal of Cancer* 2010; 46(11):1960-1966.
11. Masera G, Baez F, Biondi A, Cavalli F, Conter V, Flores A et al. North–South twinning in Paediatric haematol-oncology: the La Mascota Programme, Nicaragua. *The Lancet* 1998; 352; 1923-26
12. Arora RS, Eden T, Pizer B. The problem of treatment abandonment in children from developing countries with cancer. *Pediatr Blood Cancer* 2007;49:941-6
13. Mostert S, Arora RS, Arreola M, Bagai P, Friedrich P, Gupta S et al. Abandonment of treatment for childhood cancer: a position statement of a SIOP PODC Working Group. *The Lancet Oncology* 2011; 12(August (8):719-720
14. Mostert S, Sitaresami H, Gundy CM, Veerman AJ. Influence of socioeconomic status on childhood acute lymphoblastic leukaemia treatment in Indonesia. *Pediatrics* 2006; 118(6) e1600-e1606
15. Islam A, Akhter A, Eden T. Cost of treatment for children with acute lymphoblastic leukaemia in Bangladesh. *Journal of Cancer Policy* 2015;6 :37-43.
16. Liu Y, Chen J, Tang J, Ni S, Xue H, Pan C. Cost of childhood acute lymphoblastic leukaemia care in Shanghai, China. *Pediatric Blood and Cancer* 2009;53(4)557-562
17. Ji X, Xuan Y, Li J, Zhao J, Lu S, Zhang J, Zhao P. Direct costs for Retinoblastoma treatment during the first year of comprehensive therapy in China. *Journal of Paediatric Ophthalmology and Strabismus.* 2012; 49(6), 353-358
18. Ghatak N, Trehan A, Bansal D. Financial burden of therapy in families with a child with acute lymphoblastic leukaemia: report from North India. *Supportive Care in Cancer* 2016; 24(1) 103-108
19. Sullivan R, Kowalczyk JR, Agarwal B, Ladenstein R, Fitzgerald E, Barr R, Valsecchi M G. New policies to address the global burden of childhood cancers. *The Lancet Oncology.* 14(3);e125-e135
20. You D, Hug L, Ejdemyr S,Idele P, Hogan D, Mathers C, Alkema L. Global, regional and national levels and trends in under-5 mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Inter-agency Group for Child Mortality Estimation. *The Lancet* 2015; 386(10010):2275-2286
21. Burkitt DP. A sarcoma involving the jaws in African children, British Journal of Surgery 1958; 46218-223
22. Burkitt DP, Tunstall M. Common geography as a clue to causation. *Tropical and Geographical Medicine* 1975; 27:262-267
23. Epstein MA, Achong BG, Barr YM. Virus particles in cultured lymphoblasts from Burkitt's Lymphoma. *Lancet* 1 1964; 702-703
24. Van den Bosch CA. Is endemic Burkitt's Lymphoma an alliance between three infections and a tumour promotor? *Lancet Oncology* 2004;5(12):738-746
25. Lam KM, Syed N, Whittle H, Crawford DH. Circulating Epstein-Barr virus-carrying B cells in acute malaria
26. Chabay PA, Preciado MV. EBV primary infection in childhood and its relation to B-cell lymphoma development: a mini-review from a developing region. *Int.J.Cancer* 2013;133(6):1286-92
27. Engels EA, Biggar J, Hall HI, Cross H, Crutchfield A , Finch JL et al. Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer* 2008; 123(1):187-194
28. Mutyaba I, Phipps W, Krantz EM et al. Population-level evaluation of the effect of antiretroviral therapy on cancer incidence in Kyadondo County, Uganda, 1999-2008. *J Acquir Immune Defic Syndr.* 2015; 69(4) :481-486
29. Wabinga H, Nambooze S, Amulen PM, Okello C, Mbus L, Parkin DM. Trends in the incidence of cancer in Kampala, Uganda 1991-2010. *Int J. Cancer* 2014;135(2):432-439.
30. Cook-Mozaffari P, Newton R, Beral V, Burkitt DP. The geographical distribution of Kaposis sarcoma and of lymphomas in Africa before the AIDS epidemic. *British Journal of Cancer.* 1998; 78(11): 1521-8
31. Olp LN, Minhas V, Gondwe C.et al. Effects of antiretroviral therapy on Kaposi's Sarcoma-associated Herpes virus (KSHV) transmission among HIV-Infected Zambian children. *Journal of the National Cancer Institute* 2015; 107 (10)
32. Lee CL,Hsieh KS, Ko YC. Trends in the incidence of hepatocellular carcinoma in boys and girls in Taiwan after large scale Hepatitis B vaccination. *Cancer Epidemiology, Biomarkers and Prevention* 2003;12(1);57-9
33. Shimakawa Y, Lemoine M, Mendy M et al. Population-based interventions to reduce the public burden related with hepatitis B virus infection in the Gambia, West Africa. *Trop Med Health* 2014: 42(2 suppl):59-64
34. Chang MH, You SL, Chen CJ, Liu CJ, Lee CM, Lin SM et al. Decreased incidence of hepatocellular carcinoma in hepatitis B vaccinees: a 20 year follow-up study. *Journal of the National Cancer Institute* 2009; 101:1348-1355
35. Saha V, Love S, Eden T, Micallef-Eynaud P, Mackinlay I. Determinants of symptom interval in childhood cancer. *Archives of Disease in Childhood* 1993;68: 771-4
36. Howard SC, Wilimas JA. Delays in diagnosis and treatment of childhood cancer: where in the world are they important? *Pediatr Blood Cancer* 2005;44:303-304
37. Stefan DC, Siemonsma F. Delay and causes of delay in the diagnosis of childhood cancer in Africa. *Pediatr Blood Cancer* 2011; 56(1):80-85.
38. Poyiadjis S, Wainwright L, Naidu G, MacKinnon D, Poole J. The Saint Siluan warning signs of cancer in children: impact of education in rural South Africa. *Pediatr Blood Cancer* 2011;56:314-316
39. Hunger SP, Sung L, Howard SC. Treatment strategies and regimens of graduated intensity for Childhood Acute Lymphoblastic Leukaemia in low-income countries: A proposal: *Pediatr Blood Cancer* 2009;52:559-565
40. Israels T, Renner L, Hendricks M, Hesseling P, Howard S, Molyneux E. SIOP PODC Recommendations for Supportive Care of Children with Cancer in low-income settings. Pediatr. *Blood Cancer* 2013; 60:899-904.
41. Hesseling P, Israels T, Harif M, Chantada G, Molyneux E. Practical Recommendations for the Management of Children with Endemic Burkitt Lymphoma (BL) in a Resource Limited Setting. *Pediatr Blood Cancer* 2013;60:357-362
42. Molyneux E, Davidson A, Orem J, Hesseling P, Balagadde-Kambugu, Githanga J, Israels T. The Management of Children with Kaposi Sarcoma in Resource Limited Settings. *Pediatr Blood Cancer* 2013;60: 538-542
43. Israels T, Moreira C, Scanlan T, Molyneux E, Kampondeni S, Hesseling P et al. SIOP-PODC:Clinical Guidelines for the management of Children with Wilms Tumour in low Income settings. *Pediatr Blood Cancer* 2013;60: 5-11
44. Chantada G, Luna-Fineman S, Sitorus RS, Kruger M, Israels T, Leal C et al. SIOP-PODC Recommendations for Graduated-intensity Treatment of Retinoblastoma in Developing Countries. *Pediatr. Blood Cancer*
45. Day S, Hollis R, Challinor JM, Bevilacqua G, Bosomprah E. Baseline Standards for paediatric oncology nursing care in low to middle income countries: position statement of the SIOP-PODC Nursing Working Group. *Lancet Oncology*; 2014 Volume 15:681-682
46. Patte C, Auperin A, Michon J et al. The Societe Francaise d'Oncologie Pediatrique LMB89 Protocol: Highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphoma and L3. Leukaemia. *Blood* 2001; 97:3370-3379
47. Hesseling PB, Njume E, Kouya F, Katayi T, Wharin P, Tammannai M et al. The Cameroon 2008 Burkitt Lymphoma Protocol: Improved Event – Free Survival with Treatment Adapted to Disease- Stage and the Response to Induction Therapy. *Pediatric Hematology and Oncology* 2012;29: 119-129
48. Ngoma T, Adde M, Durosinmi M, Githang'a J, Aken'Ova Y, Kaijage J, et al (+11 other authors). Treatment of Burkitt lymphoma in equatorial Africa using a simple three-drug combination followed by a salvage regimen for patients with persistentor recurrent disease. *Br J Haematol.*2012 Sep;158(6):749-762.
49. Rahiala J, Riikonen P, Kekalainen L, Perkkio M. Cost analysis of the treatment of acute childhood lymphoblastic leukaemia according Nordic protocols. *Acta Paediatr*. 2000 ;89:482-487.
50. World Health Organization Model List of Essential Medicines for Children 5th List April 2015 (amended August 2015)-www.who.int/medicines/publications/essential medicines /en/
51. Robertson J, Magrini N, Barr R, Forte G, Ondari C. Medicines for Cancers in Children: The WHO Model for Selection of Essential Medicines . Pediatr Blood Cancer 2015;62:1689-1693
52. Barr R, Robertson J. Access to cytotoxic Medicines by Children with Cancer: A focus on low and middle income countries. Pediatr. *Blood Cancer* 2015;doi10.1002/pbc.25722.
53. Denburg A, Arora B, Arora RS, Auste C, Bagai P, Barr R, Challinor J, Eden T, Grynzspancholc E, Hoffman R, Link M. Access to essential medicines for children with cancer: a joint SIOP-CCI position statement The Lancet Oncology 2017: Volume 18(January):20-22
54. Eden T, Burns E, Chunda-Lyoka C, Dolendo M, Islam A, Khaing AA and 6 others. Are Essential Medicines Available, Reliable, and Affordable in low –Middle income countries. *Proceedings of the international Society of Paediatric Oncology October* 2015-published on line SIOP 2015 abstract SIOP5-0121
55. Clark F. Rise in online pharmacies sees counterfeit drugs go global. *The Lancet* 2015 ; 386:1327-1328

PALLIATIVE CARE FOR CHILDREN IN LOW- AND MIDDLE-INCOME COUNTRIES

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Palliative care is an important component of a cancer control programme. There is a lack of access to children's palliative care in many low- and middle-income countries (LMICs), yet the need is great. Whilst there are challenges to the development of children's palliative care many of these can be overcome, and the basic principles for cancer control can serve as a framework for the development of children's palliative care in LMICs.

Palliative Care for children is an essential component of any cancer care programme. Whilst aiming for early identification, treatment and cure is a priority, in many instances this is not possible, particularly within low- and middle-income countries (LMICs), where 70% of all cancer deaths occur *(1)*, and 80% of individuals with cancer present at an advanced stage, with limited or non-existent resources available for prevention, diagnosis and treatment *(1)*. The incidence of childhood cancer is increasing globally, with an estimated 300,000 new cases diagnosed each year: 215,000 (0–14 years) and 85,000 (15–19 years), with many more cases uncounted and unreported due to a lack of childhood cancer registries *(2)*, and approximately 90% of these children live in LMICs *(3)*. As a core component of cancer control, palliative care meets the needs of all patients requiring relief from symptoms and their families *(1)*.

What is palliative care for children?

The World Health Organization defines palliative care for children as a special, albeit closely related field, to adult palliative care:

- Palliative care for children is the active total care of the child's body, mind and spirit, and also involves giving support to the family.
- It begins when illness is diagnosed, and continues regardless of whether or not a child receives treatment directed at the disease.
- Health providers must evaluate and alleviate a child's physical, psychological, and social distress.
- Effective palliative care requires a broad multidisciplinary approach that includes the family and makes use of available community resources; it can be successfully implemented even if resources are limited.
- It can be provided in tertiary care facilities, in community health centres and even in children's homes *(4)*.

Whilst this is the definition recognized globally, Together for Short Lives *(5)*, have defined palliative care for children as "An active and total approach to care, from the point of diagnosis or recognition, throughout the child's life, death and beyond. It embraces physical, emotional, social and spiritual elements and focuses on the enhancement of quality of life for the child or young person and support for the family. It includes the management of distressing symptoms, provision of short breaks and care through death and bereavement." They also looked at the different categories of children requiring palliative care as the spectrum and severity of a child's condition, complications and the impact on the child and their family need to be considered (see Table 1) *(6)*. These categories help those providing palliative care services for children and their families to think about the different disease trajectories and when and where children may need support.

Global provision of children's palliative care

Palliative care for children is, for many, still a new concept, with provision of services being limited in many areas. A recent

Table 1: **Examples of infectious diseases in patients presenting to various healthcare settings and RDTs available**

Category 1 **Life-threatening conditions for which curative treatment may be feasible but can fail**	Access to palliative care services may be necessary when treatment fails or during an acute crisis, irrespective of the duration of threat to life. On reaching long-term remission or following successful curative treatment there is no longer a need for palliative care services. ***Examples: cancer, irreversible organ failures of heart, liver, kidney.***
Category 2 **Conditions where premature death is inevitable**	There may be long periods of intensive treatment aimed at prolonging life and allowing participation in normal activities. ***Examples: cystic fibrosis, duchenne muscular dystrophy.***
Category 3 **Progressive conditions without curative treatment options**	Treatment is exclusively palliative and may commonly extend over many years. ***Examples: batten disease, mucopolysaccharidoses.***
Category 4 **Irreversible but non-progressive conditions causing severe disability, leading to susceptibility to health complications and likelihood of premature death**	***Examples: severe cerebral palsy, multiple disabilities, such as following brain or spinal cord injury, complex healthcare needs, high risk of an unpredictable life-threatening event of episode.***
Additional proposed categories (Wood et al): Category 5 **Neonates with limited life expectancy**	
Category 6 **Members of a family having unexpectedly lost a child from a disease, an external cause or during the perinatal period**	

study looking at the global need for children's palliative care estimates that at least 21.5 children globally need access to palliative care services, with at least 8 million of these needing specialist palliative care *(7)*. Furthermore, initial analysis of need versus provision i.e. a gap analysis, suggests that in some countries such as Zimbabwe and Kenya, less than 1–5% of children in need can currently access services *(8)*, with the global estimation being that less than 10% of children in need can currently access palliative care, i.e. there are over 19 million children globally who need palliative care but cannot access services. Thus, whilst it is estimated that only 6% of the overall global need for palliative care is for children *(9)*, this still represents a global imperative for the development of children's palliative care.

A systematic review published in 2011, identified that 65.6% of countries had no known children's palliative care activity with only 5.7% having provision that was reaching mainstream providers *(10)*. This review based on the levels of palliative care provision, developed by Clark and Wright *(11)* highlighted the need for urgent development of palliative care services for children, particularly noting the need for development within low- and middle-income countries, where need is often greatest, but provision non-existent. These findings were endorsed by Connor et al's study *(7)* which found that the estimated need for children's palliative care ranged from almost 120 per 10,000 children in Zimbabwe, a low-income country with high incidence of HIV, to that in a high income country such as the United Kingdom where approximately 20 per 10,000 children need access to palliative care. Whilst HIV is a key challenge for children's palliative care, congenital anomalies and neonatal conditions account for the greatest number of children in need of palliative care at the end of life *(9)*, with those from cancer accounting for just 5.69% of the need at the end of life.

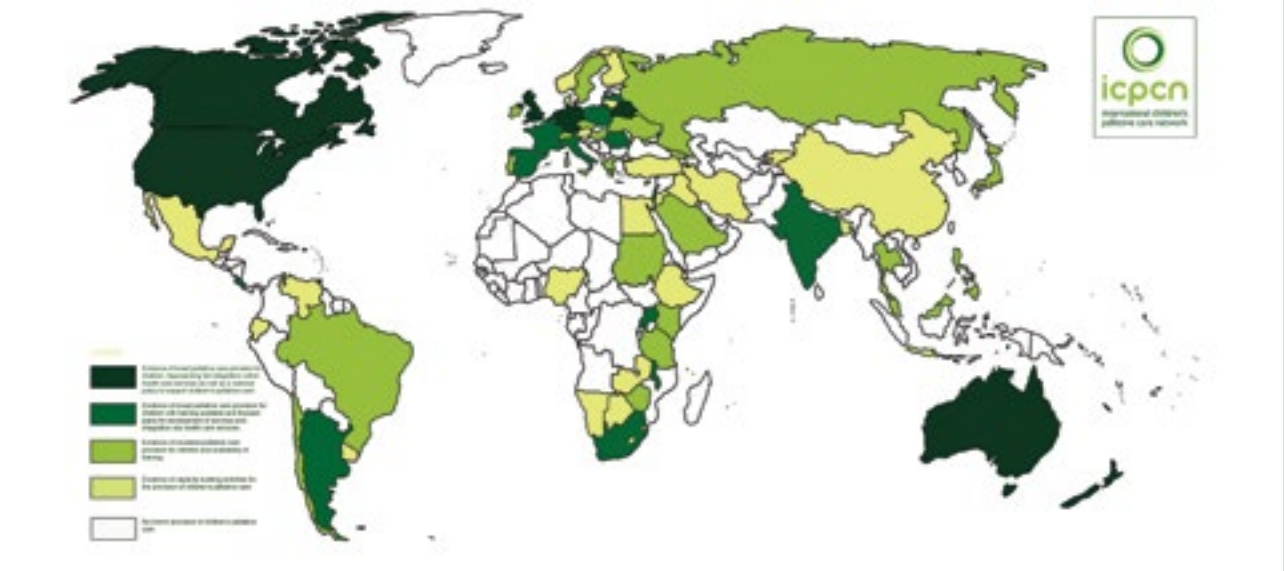
Whilst estimating the need and provision of children's palliative care can be challenging, the International Children's Palliative Care Network (ICPCN) has a directory of services globally, and estimates the provision of children's palliative care (Figure 1). From this, ICPCN has been able to track the development of children's palliative care globally, but it also shows the immense need for urgent and ongoing developments within the field across the majority of LMICs.

The International Children's Palliative Care Network

The International Children's Palliative Care Network (ICPCN) is a global network of individuals and organizations working in the field of palliative care for children. The vision of ICPCN is to achieve worldwide the best quality of life and care for children and young people with life limiting illnesses, their families and carers. Ensuring that children's palliative care is acknowledged and respected as a unique discipline within healthcare systems and provided by suitably trained and qualified people to all children with life limiting or life threatening conditions and their families, regardless of where in the world they live. Care should include services, therapies and medications that will reduce pain and suffering and encompass all their physical, social, emotional, spiritual and developmental needs and that of their families, allowing for the best possible quality of life *(12)*. ICPCN works in five key areas:

- Communication – with members, organizations,

Figure 1: **An ICPCN map showing estimates of palliative care provision**



policymakers etc. providing an international directory and mapping of services, networking opportunities, facilitating sharing of innovations and resources, provision of an up-to-date website providing a comprehensive source of information, editing the international children's edition of ehospice (website) and publishing resources and position papers on important issues related to children's palliative care.

- Advocacy – conducting advocacy at the national, international, regional and global levels depending on need and in conjunction with local and international partners. Representing children's palliative care in different fora such as the World Health Assembly, the WHO technical advisory group, the UN care and support task force, to name but a few.
- Research – co-ordinating and conducting research in different aspects of children's palliative care, such as children's understanding of illness, death and dying; the global need for children's palliative care; what makes a successful model for children's palliative care in sub-Saharan Africa; and studies looking at the 2-step vs 3-step analgesic ladder.
- Education – providing face-to-face training on children's palliative care, train the trainers and supporting the delivery of diploma, degree and masters' programmes. The provision of online e-learning training courses, endorsed by the University of South Wales and available in a variety of different languages. Covering topics such as pain assessment and management, communicating with children, bereavement, play, end-of-life care, and perinatal palliative care. Conferences are also held within LMICs, working with local partners, in order to promote the advancement of children's palliative care in that region.
- Support and development – offering strategic support and materials to individuals and organizations wishing to start children's palliative care services in their part of the world, help and advice reintegration of services, models of care, etc.

Challenges for the development of CPC in LMICs

A variety of best practice models of children's palliative care in LMICs have been described e.g. Umodzi in Queen Elizabeth Hospital in Blantyre Malawi, Yayasan Rumah Rachel (Rachel House) in Jakarta Indonesia, and the Belarusian Children's Hospice (BCH) *(13)*. However, many challenges exist in the development of palliative care for children in LMICs and these can be seen in relation to the public health approach to the development of palliative care *(14)* in the areas of policy, education, medication availability and implementation *(13)*. These include:

- A lack of policies on palliative care generally and children's palliative care specifically.
- A lack of the recognition for the need of palliative care for children, and what palliative care can offer.
- A lack of the integration of palliative care for all ages, including neonates, children and young people, into the health system.
- A lack of access to education in the countries with the greatest need, alongside a lack of access to clinical sites for the modelling of children's palliative care, and a lack of access to specialist children's palliative care training
- A lack of access to medications for palliative care, in particular to that of moderate to severe pain relieving opioids, such as oral morphine. Where the Essential

Medicines List (EML) *(15)* for palliative care has been adopted, medicines may still not be available or accessible to the children in need, and evidence suggests that access to such medicines for children is poor *(16)*.

- A lack of resources, such as financial, which impacts on the above.

Strategies for the development of CPC in LMICs

Whilst the greatest need for the development of children's palliative care is in LMICs, these are often the countries with least capacity for development, the most barriers to provision and the greatest health inequalities. The WHO sets out some basic principles for cancer control which can serve as a basis for implementing palliative care *(1)*: leadership; involvement of stakeholders; creation of partnerships; responding to the needs of people; decision-making based on evidence; seeking continuous improvement; application of a systemic integrated approach; and adoption of a stepwise approach to planning and implementation. This framework is useful in reviewing some of the core infrastructure and services needed for the development of children's palliative care in LMICs.

1) **Leadership** – i.e. the activity of leading a group of people or an organization or the ability to do this *(17)*. Leadership involves establishing a clear vision, sharing that vision with others so that they will follow; providing the information, knowledge and methods to realize the vision; co-ordinating and balancing conflicting interests of all members and stakeholders *(17)*. Leadership has been, and remains key in the ongoing development of children's palliative care. Globally, there have been individuals, such as Ann Armstrong-Daly and Sister Frances Dominica and organizations, such as ICPCN, Children's Hospice International (CHI) and Together for Short Lives, who have been recognized as the leaders within the field. ICPCN seeks to work with individual leaders from different countries to support them to lead the development of children's palliative care within their country and region. Research into what are the components contributing to a successful model of children's palliative care in sub-Saharan Africa identified that having clear and strong leadership is essential, with leadership that is focused on the vision of children's palliative care, is passionate about the cause, and empowers and enables others to follow such that there is ongoing and lasting development *(18)*. Likewise, changes in leadership along with a lack of leadership contribute to the challenges for models of children's palliative care.
2) **Involvement of stakeholders and creation of partnerships** – It is essential that we work together in partnership to achieve the aim of increasing access to and availability of children's palliative care. Together we are stronger, and there are times when the ICPCN works in partnership with organizations working more broadly in palliative care, such as the International Association of Hospice and Palliative Care (IAHPC), the Worldwide Hospice and Palliative Care Alliance (WHPCA) and the Union International for Cancer Control (UICC), such as when working together to increase access and availability to the essential medicines for palliative care – both for adults and for children. By working in partnership on this issue we have a stronger voice, particularly as we note that only about 6% of global palliative care need is for children *(9)*. Working in partnership also helps to foster an environment of mutual learning and mentorship where we can learn from each other and support each other. It is also important that developments are led from within country, thus the presence of local stakeholders is essential and ICPCN seeks to work through local, national and regional stakeholders as appropriate, thus fostering ownership and therefore ongoing sustainability of the development of children's palliative care services. Examples of partnerships include ICPCN working with World Child Cancer to support the development of CPC in Bangladesh, and also ICPCN working on an international forum with Childhood Cancer International, to promote and advocate for palliative care for all children with cancer.
3) **Responding to the needs of the people** – any palliative care service needs to respond to the palliative care needs of children and their families. Needs assessments have been carried out both in terms of the numbers of children needing palliative care within countries and the needs of children requiring palliative care e.g. in South Africa *(19)*, in Ireland *(20)*, in Serbia *(21)*. Understanding need is linked to ensuring the services respond to the needs of the community, are in touch with the environment and have a clear vision.
4) **Decision-making based on evidence and seeking continuous improvement** – unfortunately there is a lack of evidence globally within children's palliative care. A review of the status of palliative care in children in sub-Saharan Africa, found that there is very little data within the field, particularly with regards to childhood cancers in Africa, models of children's palliative care and a general lack of an evidence base for children's palliative care, with no measurement tools *(22)*. In 2012 new guidelines were published by the WHO with regards to the pharmacological treatment of persisting pain in children with medical illnesses *(23)*. One of the challenges to the development of these guidelines was the lack of evidence on the use of medications in children's palliative care, with the WHO calling on organizations to undertake research and strengthen the evidence base within children's palliative care, with ICPCN being seen as a key stakeholder

in this *(24)*. Global priorities for research on children's palliative care have been developed *(25)* and include areas around pain management, how to control pain in the absence of strong analgesics, models of palliative care development, and children's understanding of illness, death and dying – all areas of evidence important for the ongoing development of children's palliative care in LMICs. In the past, research has been seen as optional, however it is not and should be a core component of any children's palliative care services – indeed the less resources that we have, the more we need to know that we are using them in the best possible way, with the best possible outcomes. The need for a measurement tool to measure outcomes in children's palliative care has been recognized with the ongoing development of the APCA Children's Palliative Outcome Scale (APCAC-POS) *(26, 27)* which can be used both for research, but also for audit and ensuring continuous improvement.

5) **Application of a systemic integrated approach** – The importance of an integrated palliative care service was stressed within the World Health Assembly (WHA) resolution on palliative care. The resolution urges Member States to "support the comprehensive strengthening of health systems to integrate evidence-based, cost-effective and equitable palliative care services in the continuum of care, across all levels, with emphasis on primary care, community and home-based care and universal coverage schemes" *(p3 28)*. In the development of children's palliative care in LMICs there must be an integrated, co-ordinated approach. One that shows a clear strategy, is adaptable, consistent, provides different components of care through the holistic approach – all key elements that make an effective children's palliative care programme *(18)*.
6) **Adoption of a stepwise approach to planning and implementation** – The WHA resolution *(28)* recognizes the need and ongoing challenges for the provision of palliative care for all ages and recommends that palliative care should be an integral component of all relevant global disease control and health system plans, including those relating to noncommunicable diseases (NCDs) such as cancer, and universal health coverage. Thus, there needs to be clear planning in place, clear policies and an implementation plan for the development and expansion of children's palliative care that is realistic, affordable and sustainable. Services can exist as stand-alone non-profit organizations, or be aligned in government-funded hospital or academic centres, and the development of beacon centres across the region can support both service development and education *(29)*. Clear national and advocacy plans need to be developed in order to ensure the development and implementation of appropriate national policies, to ensure the availability of the essential medicines for palliative care *(30)* including paediatric formulations, and to ensure the availability of appropriate education on children's palliative care at the different levels as identified in the WHA resolution *(28)*, and in various education and competency documents such as the EAPC White Paper on core competencies for education in paediatric palliative care *(31)* and the APCA core competencies for palliative care in Africa *(32)*. Education needs to be provided in a variety of forms such as through face-to-face training, clinical placements and online training, such as the ICPCN e-learning programmes (www.elearnicpcn.org), in order to ensure that education is available to all, regardless of where they live.

Conclusion

There is a great need globally for the ongoing development of children's palliative care, particularly within LMICs, and for children with cancer, alongside those with other conditions requiring palliative care. Barriers exist to the provision of CPC in LMICs but many of these can be overcome through clear advocacy, planning and implementation. Changes to such health inequalities can be addressed through the WHO framework, and the implementation of a comprehensive cancer control programme thus increasing access in LMICs. The ICPCN, the only network working together for the development of CPC globally, is in a unique position to support this ongoing development of CPC in LMICs in order that all children, regardless of where they live, will eventually have access to culturally appropriate palliative care provision. ■

Professor Julia Downing is an experienced palliative care nurse, educationalist and researcher. She has been working within palliative care for 25 years, with 17 of those working internationally in Uganda, Africa, Eastern Europe and throughout the world developing palliative care services for adults and children. She is the Chief Executive of the ICPCN and is an Honorary Professor at Makerere University, Kampala. She serves on the Boards of several NGOs and was the recipient of the Robert Tiffany lectureship from the ISNCC in 2014, was profiled in a publication on Women as Change Agents in Oncology and was awarded an Honorary fellowship from Cardiff University in 2016.

Sue Boucher is an educator by profession, consultant editor and author of children's books and educational textbooks. She is the Director of Communications for ICPCN and oversees all activities related to communication, networking, media releases and information sharing. She manages the ICPCN website and edits the international children's edition of ehospice. She is an adviser to the Elizabeth Kübler-Ross Foundation, sits on the steering committee of PatchSA, and is a board member of Umduduzi Hospice Care for

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Busi Nkosi is the Director of Advocacy for ICPCN. She is a nurse by profession and spent 13 years working as a primary healthcare nurse for the South African Department of Health. She is also a midwife, nurse educator, manager and community health nurse. She joined the field of children's palliative care 16 years ago and started working for ICPCN in 2012. She has advocated for children's palliative care at global, regional and local levels. She regularly conducts training courses in children's palliative care in various African countries and assists with establishing CPC services in some of these countries.

Alex Daniels has worked in palliative care since 2010. As part of the Bigshoes team she provided hospital based palliative care for three Cape Town-based hospitals, including Red Cross War Memorial Children's Hospital. She played a key role in the development of an in-patient paediatric palliative care unit based at Sarah Fox Convalescent Children's Hospital in Cape Town. Alex has over 15 years of experience as a professional nurse and has considerable experience in facilitating grief and loss workshops with adult caregivers equipping them to support the bereavement needs of children. Alex joined ICPCN as education consultant in March 2017.

References

1. World Health Organization. 2006. Cancer Control: Knowledge into Action – WHO Guide for Effective Programmes. Geneva: World Health Organization
2. International Childhood Cancer Day (ICCD). 2017. The Hard Facts on Childhood Cancer… and what YOU can DO! Infographic. http://internationalchildhoodcancerday.org/assets/Cancer-InfoGraphic-English-Page-1.pdf Accessed 29 May 2017
3. Childhood Cancer International (CCI). 2017. 8 reasons why childhood cancer should be a Global Child Health Priority. http://www.childhoodcancerinternational.org/8-reasons-why-childhood-cancer-should-be-a-global-child-health-priority/ Accessed 29 May 2017
4. World Health Organization. 2017. WHO definition of palliative care. Accessed 29 May 2017 at: http://www.who.int/cancer/palliative/definition/en/
5. Together for Short Lives. 2017. Definitions: Children's Palliative Care. http://www.togetherforshortlives.org.uk/professionals/childrens_palliative_care_essentials/definitions Accessed 29 May 2017
6. Wood F, Simpson S, Barnes E et al. 2010. Disease trajectories and ACT/ RCPCH categories in paediatric palliative care. *Palliat Med* 24:796-806
7. Connor SR, Downing J, Marston J. 2017. Estimating the global need for palliative care for children: A cross-sectional analysis. *J Pain Sympt Manage.* 53(2):171-177
8. Connor SR, Sisimayi C. 2013. Assessment of the Need for Palliative Care for Children: *Three Country Report: South Africa, Kenya and Zimbabwe.* London: UNICEF and ICPCN
9. Connor SR, Sepulveda Bermedo MC (eds.). 2014. Global Atlas of Palliative Care at the End of Life. London: Worldwide Palliative Care Alliance
10. Knapp C, Woodworth L, Wright M et al. 2011. Paediatric palliative care provision around the world: a systematic review. *Pediatr Blood Cancer* 57:361-8
11. Clark D and Wright M. 2007. The International Observatory on End of Life Care: A Global View of Palliative Care Development. *J Pain Sympt Manage* 33(5):542-546
12. ICPCN. 2017. Fact Sheet. South Africa: ICPCN. http://www.icpcn.org/fact-sheets/ Accessed 29 May 2017
13. Downing J, Powell RA, Marston J et al. 2016. Children's palliative care in low and middle-income countries. *Arch Dis Child.* 101(1):85-90
14. Stjernsward J, Foley KM, Ferris FD. 2007. The public health strategy for palliative care. *J Pain Sympt Manage* 33:486-93
15. World Health Organization. 2013. Model List of Essential Medicines for Children. 4th List (April 2013) Geneva: World Health Organization. www.who.int/medicines/publications/essentialmedicines/4th_EMLc_FINAL_web_8Jul13.pdf. Accessed 29 May 2017
16. Hoppu K and Sri Ranganathan S. 2015. Essential medicines for children. *Arch Dis Child* 100 (Suppl 1):S38-S420
17. Businessdictionary.com. 2017. Leadership. http://www.businessdictionary.com/definition/leadership.html Accessed 29 May 2017.
18. Downing J, Kieffer S, Marston J, Taglieri J and Sullivan G. 2016. An evaluation of models of children's palliative care in sub Saharan Africa. Abstract Book. Differentiated care for diverse communities: 5th International African Palliative Care Conference. Kampala
19. Connor SR, Sisimayi C, Downing J et al.. 2014. Assessment of the need for palliative care for children in South Africa. *Int J Palliat Nurs* 20(3):130-134
20. Department of Health and Children and the Irish Hospice Foundation. 2005. A palliative care needs assessment for children. Ireland
21. Cunningham C and Stojanovic L. 2011. Desk Review and Situational Analysis of the Palliative Care Needs of Children in Serbia. Belgrade, Serbia
22. Harding R, Albertyn R, Sherr L. 2014. Pediatric palliative care in Sub-Saharan Africa: a systematic review of the evidence for care models, interventions and outcomes. *J Pain Sympt Manage* 47:642-51
23. World Health Organization. 2012. WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses. Geneva, Switzerland: WHO
24. Milani B, Magnini N, Gray A, Wiffen P and Scholten W. 2011. WHO Calls for Targeted research on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses. *Evid.-Based Child Health* 6:1017–1020
25. Downing J, Knapp C, Mukaden MA et al. 2015. Priorities for global research into children's palliative care: results of an International Delphi Study. *BMC Palliative Care.* 14:36
26. Downing J, Atieno M, Powell RA et al. 2012. Development of a palliative care outcome measure for children in sub-Saharan Africa: findings from early phase instrument development. *European Journal of Palliative Care.* 19(6) 292-295
27. Namisango E, Harding R, Atieno M et al..2016. Development and validation of the APCA African Children's Outcome Scale (C-POS) in sub-Saharan Africa. Abstract Book. Differentiated care for diverse communities: 5th International African Palliative Care Conference. Kampala
28. World Health Assembly. 2014. Strengthening of palliative care as a component of integrated treatment within the continuum of care. 134th session. EB134.R7
29. Downing JD, Marston J, Selwyn C, and Ross-Gakava L. 2013. Developing children's palliative care in Africa through beacon centres: lessons learnt. *BMC Palliat Care.* 12:8
30. De Lima L, Krakauer EL, Lorenz K, Praill D, Macdonald N and Doyle D. 2007. Ensuring palliative medicine availability: the development of the IAHPC list of essential medicines for palliative care. *J Pain Symptom Manage* 33(5): 521-526
31. Downing J, Ling J, Benini F, Payne S, Papadatou D. 2014. A summary of the EAPC White Paper on core competencies for education in paediatric palliative care. *European Journal of Palliative Care* 21(5):245-249
32. APCA. 2012. Core competencies: A framework of core competencies for palliative care providers in Africa. Kampala, Uganda: APCA

INTERNATIONAL NETWORK FOR CANCER TREATMENT AND RESEARCH

Building Capacity for Cancer Prevention, Treatment and Research

INCTR

ABOUT INCTR

The International Network for Cancer Treatment and Research (INCTR) is an international non-governmental organization (NG0) that was established to address a neglected global health problem – the ever increasing burden of cancer in developing countries. The founder members of INCTR included the former Institut Pasteur in Brussels and the International Union Against Cancer, now known as the Union for International Cancer Control (UICC). The National Cancer Institute in the United States provided financial and technical support and the organization began its activities in 2000. INCTR's headquarters are located in Brussels and it has offices and branches throughout the world. INCTR became an NGO in Official Relations with the World Health Organization (WHO) in January 2010.

The need for INCTR: Cancer in developing countries

Approximately 85% of the world's people live in low- or middle-income countries (LMICs). In 2012, Globocan estimated that there were approximately 14.1 million new cases of cancer and 8.2 million deaths from cancer in the world, with 65% of deaths occurring in LMIC. The number of cancer cases continues to rise across the world, but much faster in LMICs because development brings decreased mortality and with their higher fertility rates, this rapidly translates into population growth and increased numbers of patients with common diseases. The birth rate subsequently declines, although population growth continues since people live longer. Eventually birth and death rates stabilize at a much lower level of both than was the case prior to development. These demographic changes are accompanied by the adoption of unhealthy lifestyles practiced in high-income countries, particularly smoking and increasingly, overeating and a sedentary lifestyle.

Resources of all kinds for treating cancer are limited in LMICs, such that patients who develop cancer frequently lack access to a facility capable of making an accurate diagnosis and providing appropriate therapy. There is a lack of drugs, a paucity of radiation therapy facilities and very few cancer specialists or other health care workers who are needed to effectively care for cancer patients. Diagnosis may be so delayed that there is little that can be done even if the patient does finally reach a facility competent to care for them. Terminal care is not widely available, and regulations and attitudes are still largely directed towards preventing the misuse of opioids rather than relieving the pain of dying patients, such that most patients die without symptomatic relief or little or no mental or spiritual comfort. It is estimated, for example, that less than 1% of patients who need palliative care in India receive it.

INCTR is unique in that it focuses only on the developing world. It also works directly with its collaborators, sometimes visiting them many times in order to achieve its goal of helping to build sustainable capacity in LMICs in order to assist these countries in cancer prevention, early diagnosis, treatment and palliative care. It is not an advocacy organization, and all clinical projects are coordinated by a health professional. Its output is information collected in the field, lives saved by cancer prevention or treatment, and improved quality of palliative care.

Who INCTR works with

INCTR utilizes health-care professionals familiar with the problems of developing countries to enable it to achieve its goals. See Box 1.

INCTR develops local capacity within LMICs by training health-care professionals to establish "centres of excellence" in the delivery of feasible, affordable and effective care, including palliative care, that is considered "best practice" so that they, in turn, can train others within their country or region.

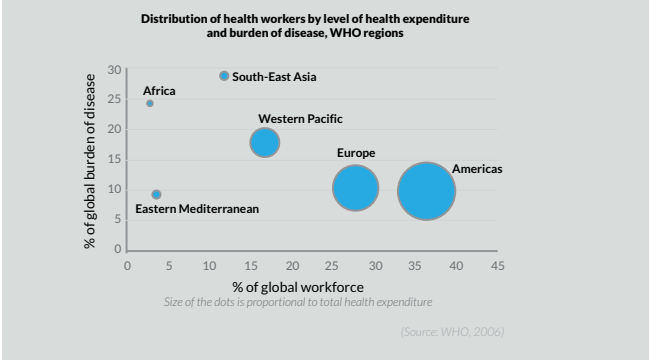
INCTR works through its branches in implementing various programmes and projects conducted in collaboration with partner institutions in developing countries and monitored by field visits.

INCTR integrates research into its programmes by documenting and evaluating actual data (rather than projected economic or health benefits, for example). Such research may include a wide range of projects, from cancer education for the general public to developing treatment outcomes, including palliative care. This, in turn, enables health-care professionals working in LMICs to become familiar with the most pressing issues and to develop plans to improve efficiency and reduce cost. Although clearly many countries have limited health workforces and quantitation of such workforces can be valuable in terms of planning for the future, it realizes that many cancer plans have little impact because of the limited

Box 1: INCTR's goals – Making a difference

- To reduce the incidence of cancer in resource-limited countries through public and professional education about the causes of cancer and how to use this information in cancer prevention
- To detect cancer early through public and professional education about the early signs of cancer and what to do if they appear
- To diagnose cancer accurately through pathology training and, where important and feasible, imaging techniques

Figure 1: Disease burden and resources



resources and great difficulty in expanding interventions to very poor populations which cannot "purchase" their own health-care needs and which have little or no chance of expanding their present resources. Having a cancer plan is not enough. Successful cancer plans require knowledge and a budget in addition to educated health professionals.

INCTR's structure

INCTR has consultants and volunteers dedicated to the accomplishment of its goals. Although its headquarters are located in Brussels, it has branches in the United States, Canada, Brazil, United Kingdom, France, Egypt, Nepal and India. Branches are legally established NGOs that contribute to and conduct programmes and projects that are relevant to INCTR's mission.

Resource development, administration and programmes (e.g., adult oncology, paediatric oncology, cancer registries, pathology and palliative care are supervised by an Executive Committee or directly by the branches. The Executive Committee is responsible to INCTR's Governing Council. Programmes and projects are developed with the participation, input and advice of various INCTR committees and strategy groups as well as independent scientific advisers. Programmes and projects are conducted in collaboration with partner institutions involved with cancer research, diagnosis and treatment, including palliative care and education in countries with limited resources.

Individuals, institutions or organizations often choose to serve as Associate Members who contribute financially to the work of INCTR.

Box 2: Strategies

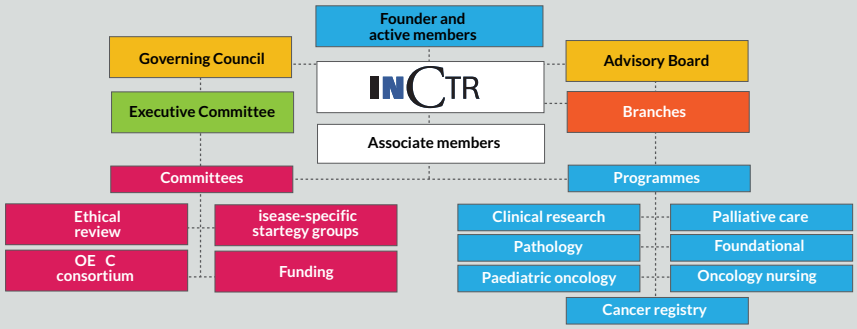
- To build capacity for cancer prevention, diagnosis, treatment and palliation through professional education and training
- To conduct, or provide materials for the conduct of educational campaigns for the public and primary care doctors about the causes of cancer and living a healthier life
- To work with experts in-country to conduct locally relevant research on cancer control

What does INCTR do?

INCTR addresses all aspects of cancer control with the overall goal of lessening the morbidity and mortality from cancer. It emphasizes training and education of health-care professionals in LMICs to ensure that "best practices" are instilled in cancer prevention, early diagnosis, treatment and palliative care. Research is an integral part of its work with its partners in LMICs in order to accurately document the cancer burden – including the types of cancer and extent of disease, the outcomes of prevention and early detection campaigns and the efficacy, toxicity and cost of treatment delivered. It also emphasizes public awareness of cancer, which is an essential component of early diagnosis. INCTR has a variety of programmes that are carried out in close collaboration with its branches as well as its partner institutions in developing countries. INCTR's current programmes include:

- adult oncology;
- cancer registry;
- clinical research;
- foundational;
- palliative care;
- paediatric oncology;
- pathology.

Figure 1: Disease burden and resources



INCTR's projects and achievements

Each INCTR programme has goals and objectives in line with the overall mission of the organization, divided into separate projects. Many projects have been conducted or are on-going and include:

Adult oncology

- Prevention, early diagnosis, and treatment of selected cancers in

poor urban areas and in rural and tribal regions in the state of Rajasthan in India.
- Cervical cancer screening using visual inspection in Nepal and Tanzania.
- Training of Bolivian health-care professionals in cervical cancer screening by Peruvian experts.
- HPV vaccination of young girls in Nepal.

Cancer registries
- Establishing an East African Registry Network (EARN) that subsequently became the African Cancer Registry Network (AFCRN). As part of the Global Initiative for Cancer Registry Development in LMICs, the Network acts as a consortium to provide a "regional hub" for cancer registries in sub-Saharan Africa. The AFCRN is supporting or assisting the development of 22 cancer registries in the region, including English-and French-speaking countries.
- Provision of training courses in cancer registration and the use of CanReg 5.
- Participation in collaborative international research.
- Visits of INCTR consultants to the Kingdom of Saudi Arabia to review cancer registration procedures and data quality and to Uganda to offer advice on setting up a cancer registry.

Clinical research
- The treatment and characterization of acute Lymphoblastic Leukemia in children, adolescents and young adults in India – over 450 patients have been treated by four institutions.
- The treatment and characterization of Burkitt Lymphoma – over 750 patients have been treated by seven centres in Nigeria, Democratic Republic of Congo, Uganda, Kenya and Tanzania. Survival is greater than 60% at 5 years.
- Understanding problems faced by parents of children with Retinoblastoma before treatment – 435 parents interviewed from institutions in 10 countries in Latin America, Asia and Africa.
- Situational analysis of breast cancer – 8,800 medical records of women treated for breast cancer in four institutions in Peru, Egypt, Pakistan and India.
- Studies carried out in Brazil, India, Pakistan and Turkey to determine delays in diagnosing and treating nasopharyngeal carcinoma and assess the role of consanguinity and familial history in this cancer.
- A new initiative to characterize the lymphoproliferative diseases in adults in Senegal with initiated in partnership with Universities in Dakar.
- Development of a pathological and radiological review for Brazilian patients with medulloblastoma in partnership with the Brazilian Society of Paediatric Oncology.

Foundational
- Accreditation Programme in the conduct of clinical trials in institutions in Brazil.
- Educating school children about cancer in Nepal.
- Evidence-based development through preparation of bibliographies of published literature from developing countries relevant to breast cancer and selected cancers in Egypt.
- Open Educational Resources for Cancer available online.
- Thematic workshops to discuss challenges in cancer control in East Africa.
- Webinars for e-learning.
- Publication of two editions of Cancer Control in 2013 and 2014 with specialist health-care publisher, Global Health Dynamics, looking at all aspects of cancer policy, prevention, detection, treatment and palliation.

Palliative care
- Training and educating health-care professionals – doctors, nurses and social workers in the principles of palliative care – in Brazil, Cameroon, Burkina Faso, Sénégal, Mali, Tanzania, India and Nepal.
- Sensitization workshops for government officials and the public in Brazil, Tanzania, India and Nepal.
- Development of a centre of excellence in palliative care for both adults and children in Hyderabad, India.
- Lobbying governments to improve access to opioids for terminally-ill cancer patients – Nepal and India.
- Establishment of twinning programmes with hospices in Canada that support palliative care efforts in Nepal.
- Fostering the establishment of palliative care societies – in Nepal and Pakistan.
- Promoting paediatric palliative care in Pakistan.
- Publishing a palliative care handbook describing the management of a wide variety of symptoms in English, Portuguese, French and Turkish.
- Development of the "Life at Your Doorstep" home care programme offering extensive, 24/7 support for patients and families struggling with advanced and terminal illness in the cities of Hyderabad and Secunderabad.
- Organized training course for Francophone sub-Saharan Africa in Uganda. This was led by HASPF and the Institute of Hospice and Palliative care in Africa with expert input by Hospice Africa Uganda and Alliance Mondial Contre le Cancer.
- Palliative care workshops and training courses for Francophone sub-Saharan Africa organized by AMCC in partnership with AFSO were held in Uganda and Ivory Coast.
- Establishment of palliative care centres of reference

and training in sub-Saharan Francophone Africa (Mali, Cameroon, Ivory Coast).
- Canadian branch provides training in India for St Mary Hospital in palliative care and fosters a collaborative approach between palliative care and health care in Nepal.
- Development of palliative care programme in Rajasthan, India.

Paediatric oncology
- Establishment of centres of reference for the treatment of retinoblastoma – Mali and Democratic Republic of Congo.
- Mentoring of Indian paediatric oncologists in the development of a common treatment protocol for Wilms Tumour.
- Conducting workshops and symposia on topics of relevance in developing countries.
- Promotion of the establishment of paediatric oncology societies – Philippines and Pakistan.
- Development of a centre of excellence in paediatric oncology at the Santa Marcelina Hospital/TUCCA in São Paulo, Brazil.
- Conducting a campaign for the early diagnosis of retinoblastoma including, but not limited to, the translation of a film showing a child with early retinoblastoma into 12 languages and distributing the film around the world (Brazil); development and wide dissemination and display of posters (Mexico and Brazil); and establishment of a retinoblastoma day (Turkey and Brazil).
- Ophthalmology nurses from the Democratic Republic of Congo trained in France to fit prosthetic eyes following enucleation (surgical removal of the eye) for the treatment of retinoblastoma.

Pathology
- Central pathology review of Burkitt Lymphoma in institutions participating in the treatment protocol for this disease in Africa.
- Training and education workshops for pathologists and clinicians.
- Training and education workshops for technicians and pathologists in techniques to improve diagnostic capabilities.
- Use of iPath – an internet telepathology programme – for consultation, training and education.
- Provision of training and education of haematopathologists in Francophone African countries (Cameroon, Democratic Republic of Congo, Sénégal).
- "What can we learn from Africa" pathology workshop held in Arusha, Tanzania for pathologists from Senegal, Benin and Democratic Republic of Congo to improve the ability of African haemato-pathologists to diagnose haematopathologocal neoplasms using the World Health Organization Classification.
- Setting up of a project to characterize lymphoproliferative disorders in adults in Senegal in partnership with local universities.
- Programme to improve pathologic and haematologic diagnostics established in Ethiopia using on-site and online training, education, and consultations.

Psychosocial support
- Development of an educational programme relating to the psychosocial needs of cancer patients in conjunction with the Brazilian Society of Paediatric Oncology.

World Health Organization
- Organized the 2009 update of the WHO Essential Medicines List for Cancer.
- Participated in guideline updating and development (cervical cancer, Kaposi sarcoma and referral guidelines for breast and cervical cancer).
- Consultation with Dr Jean Marie Dangou, Head of AFRO (African Regional Office of WHO) on non-AIDS defining malignancies in HIV positive individuals.
- INCTR organized an advisory meeting for WHO AFRO relating to the issue of AIDS-related but non-AIDS defining cancers in Africa. A report was provided to AFRO.
- Advising EMRO on a planned high-level meeting in the region late in 2014.
- INCTR is participating in the development of recommendations for the management of cancer in the Eastern Mediterranean region. INCTR's particular focus will be cancer information and the development of a tool that countries can use to identify their strengths and weaknesses with respect to cancer control, and develop or modify plans accordingly.

Considerable attention will be paid to the identification of methods of collecting and assessing the quality of data, the use of data in making scientific observations and/or the creation of evidence essential to establishing effective treatment programmes. INCTR will work more closely with governments in this regard, and funding for training, projects, scientific studies etc. will come from both within the country and outside the country. Every attempt will be made to ensure that programmes are self-sustaining after a reasonable time has passed.

INCTR BRANCHES

Branches

Branches are established as legal non-profit organizations within the country in which they are located so that they may raise and disburse funds in support of INCTR's mission. Branches establish and maintain linkages with cancer centres or units, relevant professional organizations or elements of national or regional governments and coordinate ongoing INCTR programmes and projects within the country or region, if located in a low- and middle-income country. INCTR branches are listed below.

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INCTR Brazil
Assioação International para Tratamento e Pesquisa do Cancer
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Jardim Paulista, CEP 01407-199
São Paulo, SP, Brasil
- President: Dr Sidnei Epelman

Contact: inctr@inctrbrasil.org

CANADA
INCTR Canada "Two Worlds Cancer Collaboration"
401–41 Alexander Street
Vancouver, British Columbia
V6A 1B2 CANADA
- President: Dr Simon Sutcliffe
- Treasurer: Dr Stuart Brown
- Secretary: Dr Fraser Black

Contact: cci-cancercontrol@shaw.ca or Helen@torrance.com

EGYPT
INCTR Egypt
First Floor, app 10
2 Houd El Laban Street
Garden City, Cairo, Egypt
- President: Dr Hussein Khaled
- Executive Director: Dr Atef Badran

Contact: atef.badran@gmail.com

FRANCE
Alliance Mondiale Contre le Cancer
Institut Curie, 26 Rue D'Ulm
75005 Paris, France
- President: Professor Martine Raphaël
- Medical Director: Professor Pierre Bey
- Treasurer: Professor Jacques Rouëssé
- contact@cancer-amcc.org

INDIA
INCTR India
Swasthya Kalyan Bhawan
Narin Singh Road, Jaipur
302004 Rajasthan, India
Trustees:
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- Mr Apurv Kumar
- Mr Rajiv Sahai

NEPAL
Nepalese Network for Cancer Treatment and Research INCTR Nepal Ghokechaur Banepa 1, NEPAL
- Chairman: Dr Surendra B B Shrestha
- Vice Chairman: Dr Manohar Lal Shrestha
- Member Secretary: Radha Pyari Nakarmi

Contact: nnctr@ntc.net.np

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Honorary Senior Researcher Fellow
CTSU – University of Oxford, United Kingdom

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President, AMCC, INCTR's French Branch
Hopital Bicetre
Paris, France

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Former Chief Administrator
Institut Pasteur
Brussels, Belgium

Dr Simon Sutcliffe
President, Two Worlds Cancer Collaboration
(INCTR Canada
President, Canadian Partnership Against Cancer
Vancouver, BC Canada

Ambassador for Science
Dr Harald zur Hausen
Nobel Laureate in Medicine, Deutsches Krebsforschungszentrum, Heidelberg, Germany

PARTNER INSTITUTIONS IN DEVELOPING COUNTRIES: PAST AND PRESENT

Africa

- Obafemi Awolowo University Teaching Hospitals Complex (Ile Ife, Nigeria)
- University College Hospital, Ibadan (Ibadan, Nigeria)
- Hôpital Général de Yaoundé (Yaoundé, Cameroon)
- Kenyatta National Hospital, University of Nairobi (Nairobi, Kenya)
- Bugando Medical Center (Mwanza, Tanzania)
- Muhimbili National Hospital (Dar es Salaam, Tanzania)
- Ocean Road Cancer Institute (Dar es Salaam, Tanzania)
- Tikur Anbessa Hospital, University of Addis Ababa (Addis Ababa, Ethiopia)
- St Mary's Hospital Lacor (Lacor, Uganda)
- Hôpital de Vanga (Vanga, Democratic Republic of Congo)
- Institut Ophthalmologique Tropical Africain, (Bamako, Mali)
- National Cancer Institute (Cairo, Egypt)
- Hôpital du Point G, Université de Bamako (Bamako, Mali)
- Centre Pasteur du Cameroun (Yaoundé, Cameroon)
- Université Cheikh Anta Diop (Dakar, Sénégal)
- CHU Mohammed VI (Marrakesh, Morocco)
- Clinique Universitaires, Faculté de Médecine de Kinshasa (Kinshasa, Democratic Republic of Congo)
- Clinique Universitaires, Université de Lubumbashi (Lubumashi, Democratic Republic of Congo)

America

- Santa Marcelina Hospital (Sao Paulo, Brazil)
- Instituto Nacional de Pediatria (Mexico City, Mexico)
- Instituto Nacional de Enfermedades Neoplãsicas (Lima, Peru)
- Universidad Francisco Marroquin (Guatemala City, Guatemala)
- El Instituto Oncologico Del Oriente Bolivano (Santa Cruz, Bolivia)

Asia

- Ankara University (Ankara, Turkey)
- Haceteppe University (Ankara, Turkey)
- Dokuz Eylül University (Izmir, Turkey)
- King Hussein Cancer Center (Amman, Jordan)
- King Faisal Specialist Hospital (Riyadh, Saudi Arabia)
- Children Cancer Institute, Ziauddin Medical University (Karachi, Pakistan)
- Jinnah Hospital Lahore – Allama Iqbal Medical College (Lahore, Pakistan)
- Shaukat Khanum Memorial Cancer Hospital and Research Centre (Lahore, Pakistan)
- All India Institute of Medical Sciences (New Delhi, India)
- Cancer Institute (WIA) (Chennai, India)
- Jaslok Hospital and Research Centre (Mumbai, India)
- MNJ Institute of Oncology (Hyderabad, India)
- Tata Memorial Centre (Mumbai, India)
- Nepal Institute of Health Sciences (Kathmandu, Nepal)
- B P Koirala Memorial Cancer Hospital (Bharatpur, Chitwan, Nepal)
- Bhaktapur Cancer Care Hospital (Bhaktapur, Nepal)
- Hospice Nepal (Kathmandu, Nepal)
- Kanti Children's Hospital (Kathmandu, Nepal)
- Shechan Hospice (Kathmandu, Nepal)
- Scheer Memorial Hospital (Banepa, Nepal)
- Patan Hospital (Kathmandu, Nepal)
- Philippine Children's Medical Center (Quezon City, Philippines)
- Shanghai Children's Hospital (Shanghai, China)
- Sarawak General Hospital and Sarawak Hospice Society (Kuching, Sarawak, Malaysia)

Latin America

- Santa Marcelina Hospital (Sao Paulo, Brazil)
- Instituto Nacional de Pediatria (Mexico City, Mexico)
- Instituto Nacional de Enfermedades Neoplãsicas (Lima, Peru)
- Universidad Francisco Marroquin (Guatemala City, Guatemala)
- El Instituto Oncologico Del Oriente Bolivano (Santa Cruz, Bolivia)

PARTNERS: PAST AND PRESENT

ORGANIZATIONS

World Health Organization (NGO in Official Relations)
International Agency for Research on Cancer
International Atomic Energy Agency/PACT
Union for International Cancer Control
European School of Oncology
European Society of Medical Oncology

NGOs

American Cancer Society
The Australian Cervical Cancer Foundation
Augusta Victoria Hospital
Breast Global Health Initiative
Doris Duke Charitable Foundation
Global Giving
Hospice Africa France
ICEDOC
Jiv Daya Foundation
Open Society Institute
The Aslan Project
TUCCA

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Imperial College, Hammersmith Hospital, London, UK
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King's College Health Partners, London, UK
Nainamo Hospice, British Columbia, Canada
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University of Basel, Switzerland
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Cancer Control

"The World Health Organization warmly welcomes this first annual publication on cancer control, with its laudable aim of improving cancer management in low- and middle-income countries. The publication deliberately seeks to apply the world's best expertise in cancer control, from renowned research institutes and international groups, to real conditions and needs in the developing world. It further benefits from the frontline experiences of initiatives addressing these needs and finding solutions to seemingly intractable problems."

Dr Margaret Chan,
Director-General, World Health Organization

"It is a relief to many of us working in global health to see the momentum now gathering around the global movement against cancer and other noncommunicable diseases. This latest edition of Cancer Control reflects, and is an important part of, that movement"

Dr Ala Alwan,
WHO Regional Director for the Eastern Mediterranean

***Cancer Control*, produced in association with the International Network for Cancer Treatment and Research, has established itself as one of the leading annual publications covering all aspects of cancer care as it affects emerging health systems.**

The fifth edition, Cancer Control 2017, includes the following subjects:

- **Cancer resolution 2017: Driving national action in the countdown to 2025**
- **Increasing access to cancer care: How can we guide and track actions by pharmaceutical companies?**
- **Tackling the burden of cervical cancer: Lessons from Malawi and other low- and middle-income countries**
- **Implementing a cervical cancer prevention service platform in Zambia, from scratch**
- **African HPV pathology and control: The work of the WAKA network**
- **Ending cervical cancer in our lifetime: The contribution of Pink Ribbon Red Ribbon**
- **Downstaging breast cancer in sub-Saharan Africa: A realistic target?**
- **Cancer prevention and control in the Caribbean**
- **Cancer in the commonwealth**
- **Palliative care for children in low- and middle-income countries**

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