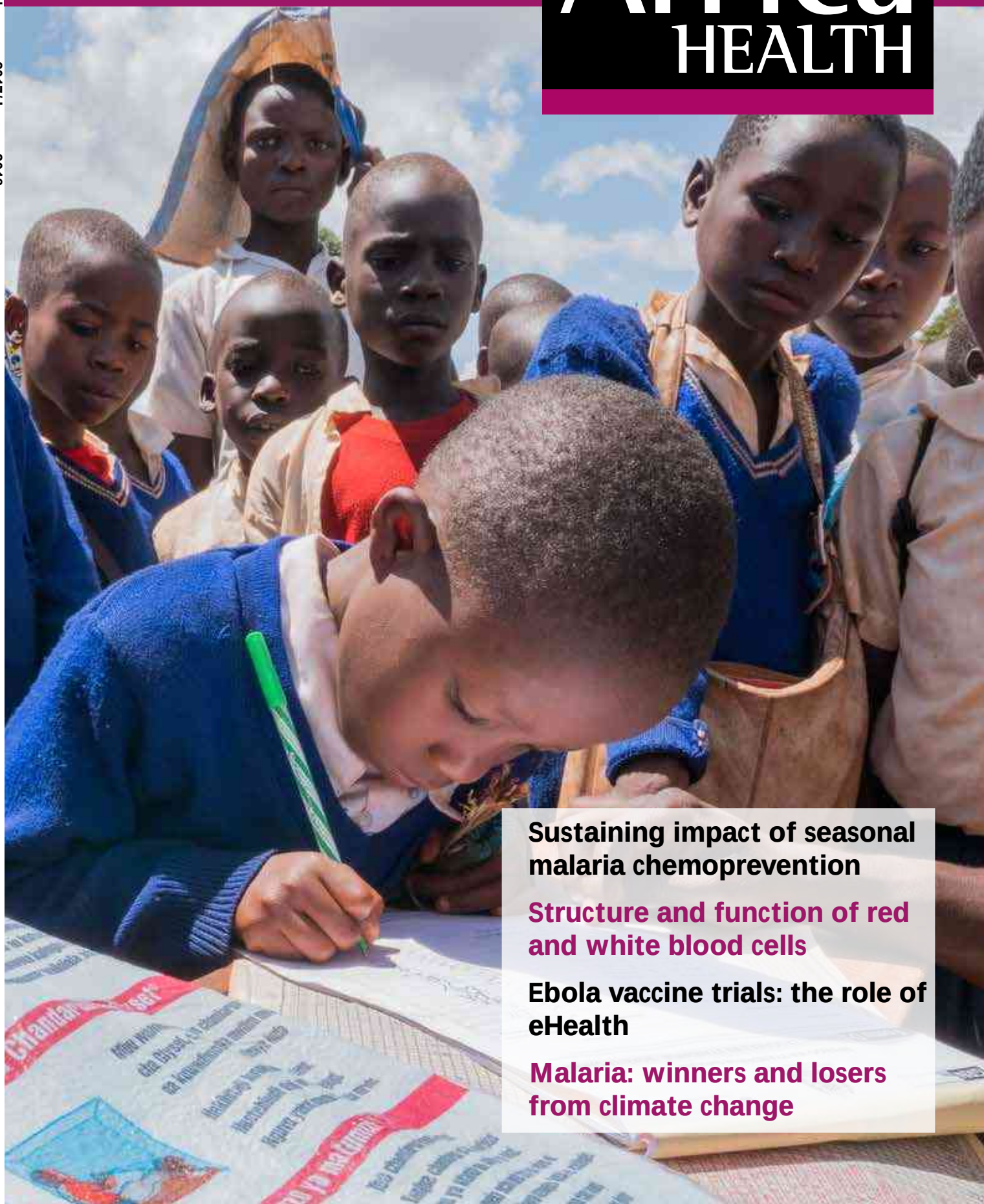
November 2017/January 2018 Volume 40 Number 1

Africa HEALTH



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Structure and function of red and white blood cells

Ebola vaccine trials: the role of eHealth

Malaria: winners and losers from climate change

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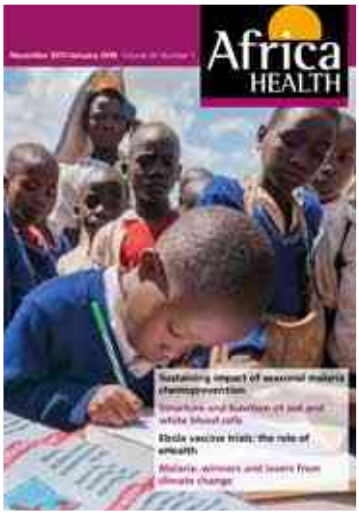

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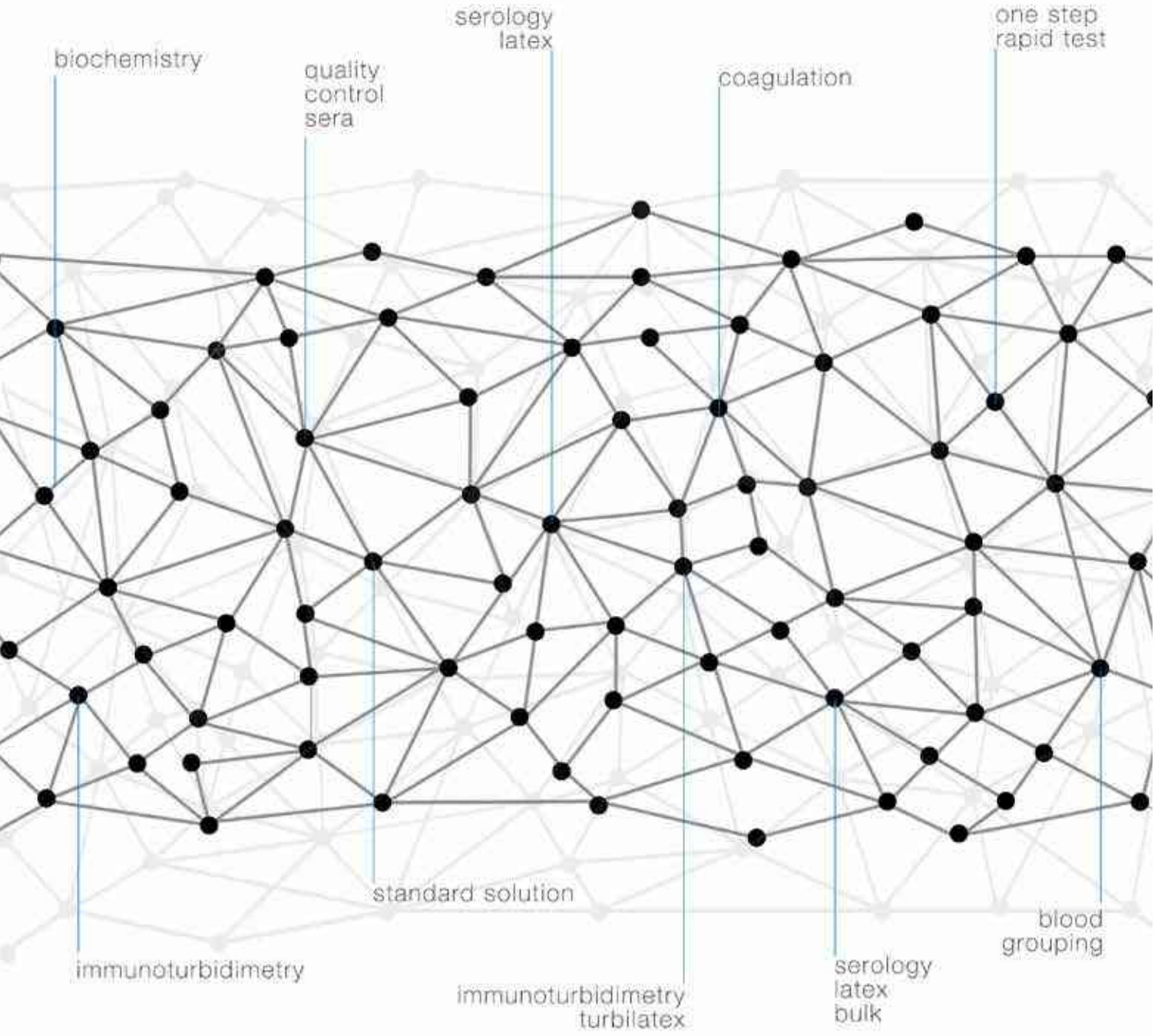

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When there is no doctor

The 4th WHO Forum on Human Resources of Health took place in Dublin in November. I'd attended the first two and went along again hoping to witness some significant progress. Sadly I came away underwhelmed. There is a lot going on in the sector, and the King of HRH, Francis Omaswa, talks positively about his takeaways from the conference in his column on page seven of this issue; but for me Africa remains in a very vulnerable position and unless there is a sea-change in the global approach to health workforce issues our condition is not going to improve. The big thinking is all going on at the community workforce level with many excellent papers emanating from research and projects coordinated and funded by the big agencies in the sector. But all too often the community workers are expected to do their vital work for no financial reward, and who is going to supervise them when the agencies have gone? In many cases, there remains a lack of integration with the traditional doctor/nurse led team. And there's the rub. There is a lack of attention being paid to the migration of these cadres who form the backbone of the physical care of patients.

Migration is not going to go away; in fact, I believe it is going to get worse. So either we have to find a way to monetise the training, which can help boost conditions of service and facilities for those who stay behind, or… to put it very bluntly… Africa's public sector health services are not going to progress, and neither will the training institutions which are screaming out for better public funding.

An alternative of course is for governments across the continent to start adhering to the Abuja Declaration they all signed up to in 2001 and commit 15% of GDP to the health budget. But the recent revelation that during the financially frothy period of the MDGs, the spend by Africa's ministries of health actually reduced, brings little comfort to any notion that the Abuja Declaration commitment might be met.

At the last count, eight countries in Africa saw major strikes by doctors or nurses during 2017. The latest strike by physicians in Uganda is on hold, waiting to see whether the government will implement the settlement deal. Kenya's health service was seriously undermined by long strikes during the year, first by nurses, and then by doctors. The common thread: pay, conditions, and respect.

Private sector healthcare in Africa is moving positively. But public sector care in many countries will not survive much more of the same old formulae. Change has to come if care for the ordinary African is to approach a satisfactory status.

And finally, a reference to mHealth. I've commented in this column in the past on the plethora of 'solutions' and the inability to scale any of them. A recent study by IQVIA claims that there are 318,000 healthcare apps now available! The fog just gets denser.

Bryan Pearson
(bryan@fsg.co.uk)

I need you here...

Taking your HIV medication EVERY DAY can help you be here when I grow up. I heard there's a "Triple Pill" that can make it easier.

Take a Triple a Day.
Every Day.

Ask your Doctor if there is a Triple Pill for YOU.

The 2014 Namibian Guidelines for Antiretroviral Therapy and The World Health Organization recommend Fixed-Dose Combination Therapy
Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection, Geneva, World Health Organization, 2013, (http://www.who.int/hiv/pub/guidelines/arv2013/en)

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I am your **Dr**obot… Repeat after me…

Computer technology has become a serious option for tackling the shortage of medical manpower. Shima Gyoh wonders if it is feasible for robots to replace doctors

The doctor's work involves the processing of enormous amounts of clinical data, often learnt over many years and needing continuous updating as it daily increases with output from many research publications. Medical technologies and the understanding of pathologies have become deep and complex, and the volume of knowledge is encyclopaedic. The human body has many systems working in an integrated fashion, and disorder of one can adversely affect the function of the others. To reach the correct diagnosis, the expert clinician has to be familiar with a vast number of clinical conditions usually learned over many years for his or her diagnosis to become reliable.

Such huge volumes of data, taken from thousands of sources, can be installed, integrated and manipulated in computers. Computer-aided diagnosis has been with us for some time. Scans can be built into smart phones or even domestic furniture to provide clinicians with health data. Where diagnosis is attempted, machine language, operating on a set of rules, selects conditional pathways to reach conclusions. The accuracy of computer-aided diagnosis depends on the skill of the doctor in manipulating the machine, but the programme itself remains unchanged until upgraded.

The human brain works differently, through a learning process. In interacting with the environment, it makes and breaks millions of inter-connecting pathways through synapses, and retentive memory is achieved through signals repeatedly going through the relevant circuits and strengthening and stabilising the synaptic connections. Its accuracy improves with increasing use or 'experience'.

This style is being imitated in computers to produce artificial intelligence (AI) by using vastly increased connections and circuits called 'neural networks'. While it takes years for humans to accumulate a large amount of medical data from which correct diagnoses can proceed, this data can be installed in a computer within a short time. In astronomy, analysis of complex data that takes trained experts months can be accomplished by AI in a split second.[1] Some companies are perfecting diagnostic machine-learning algorithms that would enable a robot to read patients' medical records, access its own internal encyclopaedic knowledge of clinical conditions taken from textbooks, journals, and medical databases to reach an accurate diagnosis. Integration of natural language processing would enable it to converse with patients and doctors, seeking clarification where necessary and answering questions.

When it comes to making diagnosis from investigations, such as histological slides, cardiograms, radiology and other forms of scanning, the performance of AI is remarkable and often much better than that of humans. Digitised images can be fed directly into algorithms. Prognosis too will be improved. In cases where there are clear dividing lines like benign and malignant, as with recognition of lesions, algorithms are often more accurate than humans. In other cases, like sepsis or arthritis, their role is limited.

One problem with the use of diagnostic scanning with AI machines might be that they will find very early malignant changes that, left alone, the immune system might subsequently destroy, or which otherwise might not proceed to clinical disease. In the prostate, for example, radical operations might result in the unpleasant complications of urinary incontinence and impotence for carcinoma in situ that might not have spread.

With regard to the speculation that AI might finally replace radiologists and pathologists, I am convinced that they will instead become powerful instruments in the hands of experts and clinicians, enabling them to increase their output with fewer staff. This would be great, particularly for the unpopular specialties always short of staff. Clinicians will also benefit as robots might take the histories and assemble the results of investigations before presentation. Despite this, palpation of clinical disease in organs, their consistency, and the general appearance and morale of the patient will still need the human touch for the foreseeable future.

Nearly all patients need the reassurance of the doctor. Many visit their physicians for support, comfort and advice, sometimes on matters not related to physical health. We also handle hypochondriacs without upsetting their health with inappropriate prescriptions. Robots can assist in all procedures, but the legal liability remains with the patient's human doctor. The best doctor is the one who is the patient's friend and confidant, and I wonder how many people would trust a robot to that extent.

Shima Gyoh has held many posts ranging from village doctor to DG of Nigeria's Federal Ministry of Health and Chair of the Medical and Dental Council of Nigeria.

Reference

1 Neural Networks meet Space, By Manuel Gnida, Symmetry, 08/30/17, www.symmetrymagazine.org/article/neural-networks-meet-space

Shining a light on severe malaria

The Severe Malaria Observatory (SMO) is a repository of information on severe malaria. It aims to:

- Disseminate best practice, tool-kits, market information, guidelines, projects and outcomes
- Advocate continuous research and capacity building
- Support visibility and coordination of ongoing activities

To enhance its impact, the SMO needs YOU.

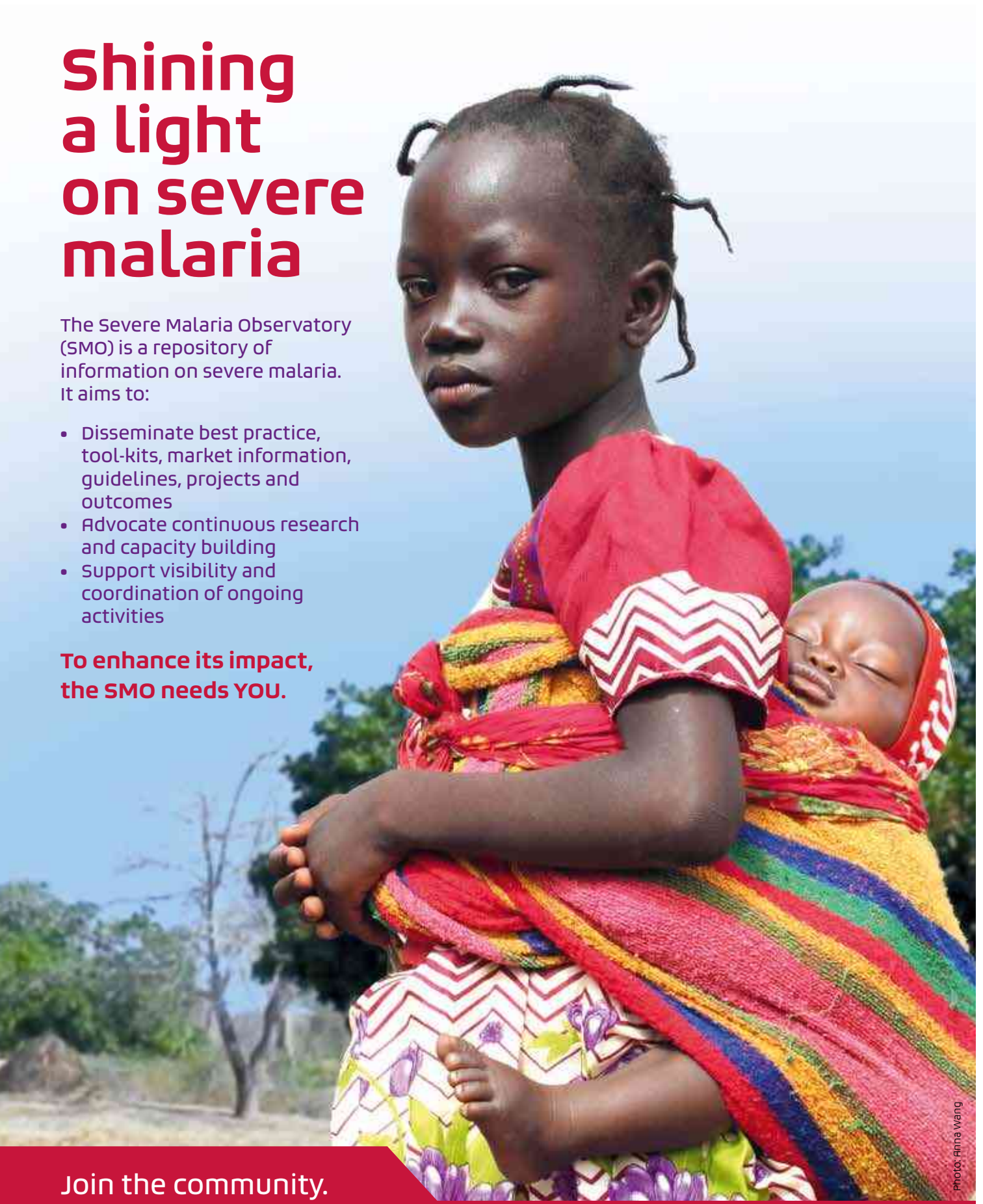

Photo: Anna Wang

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Severe Malaria Observatory

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Health workforce alive and kicking!

Francis Omaswa is heartened that health workforce debate and discussion remains strong, even if long-term solutions remain elusive

The 4th Global forum on Human Resources for Health (HRH) took place in Dublin, Ireland 13-17 November, 2017 and was attended by over 1,000 delegates from over 70 countries, representing government leaders, civil society, academia, employers, foundations, health-care professional associations and unions, youth and the private sector. Previous meetings were held in Kampala, Bangkok, and Recife in Brazil.

I organised the first Global HRH Forum in Kampala in 2008 as the Executive Director of the Global Health Workforce Alliance at the time and have attended all these Forums. I was thrilled to witness in Dublin how the HRH movement remains alive and vibrant ten years down the road.

The following were in my view the most significant outcomes of the Dublin Forum.

First is the renewal and rejuvenation of the global HRH movement representing champions committed to pursuing the call to provide a skilled, supported and motivated health worker for every person in every village everywhere and the Kampala call for 'Health Workers for All and All for Health Workers'. The achievement of this aspiration is central to the achievement of SDG 3 including Universal Health Coverage. It is this movement that will ensure that access to essential health services is not left to market forces alone which would leave many unable basic health services. Supporting this movement included the discussions around the governance of the Global Health Workforce Network (GHWN) that will bring together the stakeholders and is hosted within WHO Geneva as a successor to GHWA. GHWN activities will be implemented by Hubs in various fields, including education and training, leadership and governance, labour markets and civil society. A new Civil Society Coalition on HRH was launched in Dublin.

The participation of Africans at this Forum was strong from all parts of Africa. The African Platform on HRH held a side event which adopted a Business plan and elected a new governing board. The new Board was empowered to update the Constitution and to convene the 6th African HRH Platform Forum.

Another significant outcome was the start of the implementation of the UN Secretary General's High-Level Commission of Health Employment and Economic Growth that demonstrated that the health sector and employment in health is not just a cost but a significant contributor to economic growth and employment of women. The GDP of developed countries all enjoy significant contributions from the health sector. A new international fund named 'Working for Health Multi-Partner Trust Fund (MPTF)' will help countries expand and transform their health workforce. The MPTF will enable development partners to pool funding to be used by pathfinder countries on innovative ways to build a fit for purpose health workforce. Countries struggling to provide access to health care and where the threat of emerging epidemics is greatest are also expected to benefit. The fund is part of collaboration between the International Labour Organisation, the Organization for Economic Co-operation and Development and the World Health Organization (WHO). The Government of Norway announced its commitment to the MPTF and urged other donors to invest in the programme.

Another outcome was the launch of the International Platform on Health Worker Mobility to maximise mutual benefits and mitigate adverse effects from the increasing rate and complexity of health labour mobility, through strengthened evidence, analysis, knowledge exchange and policy action, including strengthening the WHO Global Code of Practice on International Recruitment of Health Personnel and its implementation.

A special feature not seen at previous fora was a Youth Forum which recognises that attracting and retaining young health workers is critical to averting the shortfall of 18 million health workers, and for transforming the health and social workforce. The Youth Forum agreed on their own call for action.

The Forum also committed to improving the safety and security of health workers by upholding international humanitarian law, strongly condemning violence, attacks and threats directed against medical personnel and facilities. Such attacks have long-term consequences for the civilian populations and health-care systems of the countries concerned, as well as for the neighbouring regions.

Finally, one of the most powerful take away messaged for me is that this Forum was taking place during a Doctors strike in Uganda; and last year in Kenya there was a similar strike. The Forum was told by several speakers that in rich countries money is chasing health workers, yet in most African countries, it is health workers that are chasing money. Unless action is taken to address the imbalance between the rich and poor countries, Africa will end up a donor of health workers to the rich countries.

Francis Omaswa, CEO, African Centre for Global Health and Social Transformation (based from Kampala); Founding Executive Director of the Global Health Workforce Alliance.

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The website includes:

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- Latest news
- The TRIP searchable database for evidence based articles and guidelines
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- Conference and meetings calendar
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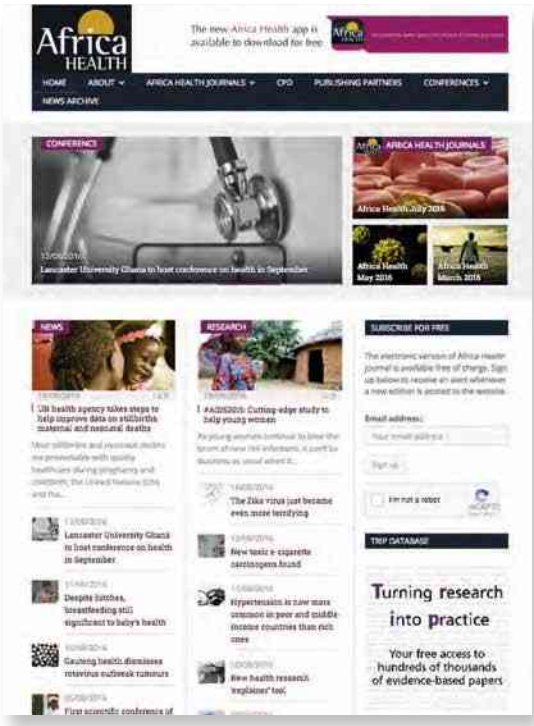

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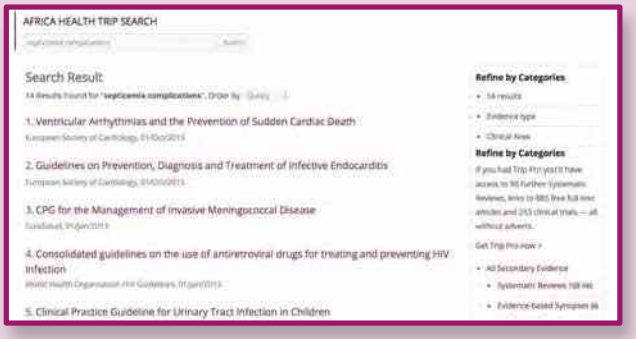

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Experts ramp up efforts to leave no one behind

With growing momentum to ensure that everyone has access to good quality health, planning experts from 27 countries of the Region met in Brazzaville to agree on how to implement a Framework of Action adopted by African ministers of health at their annual meeting in August.

The Framework presents a holistic approach to strengthening health systems to improve people's health. It sets out a menu of options that countries can consider based on their specific needs as they strive to attain the sustainable development goals (SDGs) to leave no one behind.

'The SDGs presents us with a unique opportunity for a paradigm shift in strengthening health systems across all areas focusing on integrated people-centred service delivery,' said Dr Delanyo Dovlo, Director of the Health Systems Strengthening and Services Cluster. 'As African countries prioritise universal health coverage in their health development agenda, countries need to take ownership of identifying their needs and implement the right interventions to build health systems that will achieve better outcomes and ultimately contribute to the attainment of the SDGs,' he added.

The African Region has witnessed significant improvements in population health outcomes, but these gains are not uniform across or within countries and are not always sustainable. The Region is also faced with major demographic, economic, epidemiologic, and socio-cultural transitions as well as health security and environmental threats which place great demands on health systems.

The framework, endorsed by ministers of health, is rooted in an integrated approach to systems strengthening, with a focus on communities and districts. It also provides an approach to investing in health system strengthening.

Participants reviewed the methods and tools to be used to monitor the implementation of the framework. They also agreed on the technical support needed by counties and partners from WHO. It is expected that the implementation of the framework will provide a common a approach for scheduling investments and monitoring operational as well as overall progress in the Region.

Falsified and substandard medicines continue to threaten lives of Africans

An estimated one in ten medical products circulating in low- and middle-income countries is either substandard or falsified, according to new research from the World Health Organization.

This means that people are taking medicines that fail to treat or prevent disease. Not only is this a waste of money for individuals and health systems that purchase these products, but substandard or falsified medical products can cause serious illness or even death.

'Substandard and falsified medicines particularly affect the most vulnerable communities,' says Dr Tedros Adhanom Ghebreyesus, WHO Director-General. 'This is unacceptable. Countries have agreed on measures at the global level – it is time to translate them into tangible action.'

Since 2013, WHO has received 1,500 reports of cases of substandard or falsified products. Of these, antimalarials and antibiotics are the most commonly reported. Most of the reports (42%) come from sub-Saharan Africa, 21% from the Americas and 21% from the European region. This is likely just a small fraction of the total problem and many cases may be going unreported.

'Many of these products, like antibiotics, are vital for people's survival and wellbeing,' says Dr Mariângela Simão, Assistant Director-General for Access to Medicines, Vaccines and Pharmaceuticals at WHO. 'Substandard or falsified medicines not only have a tragic impact on individual patients and their families, but also are a threat to antimicrobial resistance, adding to the worrying trend of medicines losing their power to treat.'

Before 2013, there was no global reporting of this information. Since WHO established the Global Surveillance and Monitoring System for substandard and falsified products, many countries are now active in reporting suspicious medicines, vaccines and medical devices. WHO has trained 550 regulators from 141 countries to detect and respond to this issue.

In conjunction with the first report from the Global Surveillance and Monitoring System published today, WHO is publishing research that estimates a 10.5% failure rate in all medical products used in low- and middle-income countries.

Based on 10% estimates of substandard and falsified medicines, a modelling exercise developed by the University of Edinburgh estimates that 72,000 to 169,000 children may be dying each year from pneumonia due to substandard and falsified antibiotics. A second model by the London School of Hygiene and Tropical Medicine estimates that 116,000 (64,000-158,000) additional deaths from malaria could be caused every year by substandard and falsified antimalarials in sub-Saharan Africa, with a cost of US$38.5 million ($21.4 to $52.4 million) to patients and health providers for further care due to failure of treatment.

Substandard medical products reach patients when the tools and technical capacity to enforce quality standards in manufacturing, supply and distribution are limited. Falsified products, on the other hand, tend to circulate where inadequate regulation and governance are compounded by unethical practice by wholesalers, distributors, retailers and health care workers. A high proportion of cases reported to WHO occur in countries with constrained access to medical products.

Modern purchasing models such as online pharmacies can easily circumvent regulatory oversight. These are especially popular in high-income countries, but more research is needed to determine the proportion and impact of sales of substandard or falsified medical products.

Globalisation is making it harder to regulate medical products. Many falsifiers manufacture and print packaging in different countries, shipping components to a final destination where they are assembled and distributed. Sometimes, offshore companies and bank accounts have been used to facilitate the sale of falsified medicines.

Dramatic drop in global measles cases

In 2016, an estimated 90,000 people died from measles – an 84% drop from more than 550,000 deaths in 2000 – according to a new report published by leading health organisations. This marks the first time global measles deaths have fallen below 100,000 per year.

'Saving an average of 1.3 million lives per year through measles vaccine is an incredible achievement and makes a world free of measles seem possible, even probable, in our lifetime,' says Dr Robert Linkins, of the Measles and Rubella Initiative (MR&I) and Branch Chief of Accelerated Disease Control and Vaccine Preventable Diseases at the Centers for Disease Control and Prevention. M&RI is a partnership formed in 2001 of the American Red Cross, the US Centers for Disease Control and Prevention, the United Nations Foundation, UNICEF, and WHO.

Since 2000, an estimated 5.5 billion doses of measles-containing vaccines have been provided to children through routine immunisation services and mass vaccination campaigns, saving an estimated 20.4 million lives.

'We have seen a substantial drop in measles deaths for more than two decades, but now we must strive to reach zero measles cases,' says Dr Jean-Marie Okwo-Bele, Director of WHO's Department of Immunization, Vaccines and Biologicals. 'Measles elimination will only be reached if measles vaccines reach every child, everywhere.'

The world is still far from reaching regional measles elimination goals. Coverage with the first of two required doses of measles vaccine has stalled at approximately 85% since 2009, far short of the 95% coverage needed to stop measles infections, and coverage with the second dose, despite recent increases, was only 64% in 2016.

Far too many children – 20.8 million – are still missing their first measles vaccine dose. More than half of these unvaccinated children live in six countries: Nigeria (3.3 million), India (2.9 million), Pakistan (2.0 million), Indonesia (1.2 million), Ethiopia (0.9 million), and Democratic Republic of the Congo (0.7 million). Since measles is a highly contagious viral disease, large outbreaks continue to occur in these and other countries in Europe and North America, putting children at risk of severe health complications such as pneumonia, diarrhoea, encephalitis, blindness, and death.

Agencies noted that progress in reaching measles elimination could be reversed when polio-funded resources supporting routine immunisation services, measles and rubella vaccination campaigns, and surveillance, diminish and disappear following polio eradication. Countries with the greatest number of measles deaths rely most heavily on polio-funded resources and are at highest risk of reversing progress after polio eradication is achieved.

'This remarkable drop in measles deaths is the culmination of years of hard work by health workers, governments and development agencies to vaccinate millions of children in the world's poorest countries,' said Dr Seth Berkley, CEO of Gavi, the Vaccine Alliance, one of the world's largest supporters of measles immunisation programmes. 'However we cannot afford to be complacent. Too many children are still missing out on lifesaving vaccines. To reach these children and set ourselves on a realistic road to measles elimination we need to dramatically improve routine immunisation backed by strong health systems.'

Nigeria suffering exodus

The Nigerian Medical Association Lagos State chapter has raised the alarm over the number of doctors quitting leading medical institutions. NMA Lagos State Chair Dr Olumuyiwa Odusote says that more than 40,000 of the 75,000 registered Nigerian doctors are practicing abroad while 70% of those still in the country are actively seeking jobs outside. According to him over 100 doctors resigned from UCH Ibadan in 2017, while about 800 doctors have resigned from Lagos State hospitals in the last two years.

AI app debuts for Zambian HIV patients

An intelligent app to assist in the treatment and management of HIV patients has been launched in Zambia. Significant anticipation surrounds the development as if successful, the technology could be extended to assist with other disease management.

Developed for the Zambian Ministry of Health by two teams from the Clinton Health Access Initiative, it avoids the more usual approach of digitizing volumes of existing guidelines, and instead employs elements of Human-Machine Learning. In other words it shifts the focus onto the creation of an app that is configured and programmed firstly to understand large volumes of guideline-content and then to intelligently apply this knowledge to specific patient needs within a consultation. The result, the developers hope, is an app that can be used by any health worker, and from simple data gleaned can understand the needs of a particular patient, and then quickly provide a concise response on next treatment steps required.

Just launched in Zambia, ZamCG is viewable on the Google Play store and will soon be available from the Apple and iOS stores.

Uganda doctors return to work

In late November, Ugandan doctors voted to suspend their month-long strike for three weeks following government commitment to increase salaries and improve the working conditions in public hospitals by next month. A total of 113 doctors out of 195 who attended the Uganda Medical Association (UMA) extraordinary meeting held in the capital Kampala voted to suspend the increasingly acrimonious strike. Ekwaro Obuku, the UMA president, said if the government fails to honour its commitment to respond to their issues by Dec. 15, the doctors will resume the industrial action. 'We are putting government on notice. The government shouldn't take our trust for granted,' said Obuku.

Tedros outlines progress to the WHO Executive Board

The World Health Organization's new DG, Dr Tedros Adhanom Gebrejesus recently addressed his Board. Herewith an abridged version of this speech.

'As you know, WHO has come in for criticism in recent years. Some of it fair, some of it not. Some people have questioned whether WHO is still relevant; they have asked whether we still have a role to play. We should not be afraid of hard questions. They force us to examine ourselves and do better. In the past 143 days we have already made a lot of progress. We have worked day and night, with a real sense of urgency.

'Let me give you 10 highlights. First, the General Programme of Work (GPW) was completed by mid-August, and has been discussed with all Member States, at each of the Regional Committee meetings. Second, the transformation plan and architecture has been completed and agreed with the Regional Directors, and ready for consultation. Third, a new resource mobilisation strategy has been drafted.

'Number four, building on the work of Dr Margaret Chan, we have continued to strengthen our response to emergencies at all three levels of the organisation. In one month, we were able to bring plague in Madagascar under control. Together with our partners in Bangladesh, we conducted the second-biggest oral cholera vaccination programme in history. In Uganda, we helped stamp out an outbreak of Marburg virus disease. I now receive a daily report on the status of all health emergencies. And we have instituted the WHO Health Security Council, a fortnightly meeting dedicated solely to emergencies.

'Number five, we have taken action to ramp up the response to non-communicable diseases. The Global Conference on NCDs in Montevideo has generated unprecedented political momentum as we head towards next year's UN High-Level Meeting on NCDs. And we have established a new High-Level Commission on NCDs, to be chaired by President Tabaré Vazquez of Uruguay and Dr Sania Nishtar of Pakistan. Number six, at the COP23 meeting in Bonn earlier this month, we launched our new initiative on climate change in small island developing states, and we have signed a memorandum of understanding with UNFCCC to strengthen our collaboration.

'Number seven, in October I appointed the most diverse senior leadership team in WHO's history. For the first time, women outnumber men in our top ranks. Every region is represented, ensuring that nobody is left behind in our decision-making processes. Number eight, we have stepped up our (bilateral and multilateral) political engagement.

'And number ten, just a few weeks ago, we met with all our country representatives to identify challenges and solutions.

'Currently, WHO is responding to 44 health emergencies around the world, 9 of which are grade 3 emergencies involving all 3 levels of the organisation. None are simple health problems with simple solutions. All are complex issues, involving conflict, politics, civil strife and other factors.

'The burden of non-communicable diseases continues to grow, as multinational companies market products that are harmful to health with little or no regulation. Antimicrobial resistance threatens to return us to the dark ages of medicine.

'People today live longer than at any time in human history. Life expectancy in Africa, for instance, has increased by 10 years since 2000. We have made huge gains in the fight against HIV, malaria and TB. Maternal and child mortality have dropped by half since 1990. But there are still massive disparities, and new challenges. To address these challenges, we cannot do business as usual. We need a paradigm shift, a radical change in approach. In addition to changing disease patterns and geopolitical shifts, the global health architecture has changed dramatically. So must we.

'That's what the General Plan of Work is all about. Its aim is to give birth to a WHO that has the clarity of mission to truly fulfil its mandate. It's ambitious, and it must be; we cannot afford to aim low. This GPW is not just about transforming WHO. It's about transforming global health, and ultimately transforming human lives – it's about people.

'It starts by clarifying our mission: To promote health, keep the world safe, and serve the vulnerable. It also outlines the several strategic shifts that we must make as an organisation if we are to achieve our mission. First, we must become far more focused on impact and outcomes, instead of processes and outputs.

'This requires obvious investments in metrics and measurement. To make progress, we must be able to measure progress. As you know, we have proposed the '3 billion' targets: 1 billion more people with health coverage; 1 billion people made safer; 1 billion lives improved. Of course, these targets must not be arbitrary. That's why we are appointing a reference group of experts to ensure and scrutinise that they are methodologically sound.

'The second major shift is that we must be much more vocal and visible as a global health leader, by advocating for health at the highest political levels.

'Third, WHO must become more operational and relevant in all 194 countries. We must reorient WHO to put countries at the centre of everything we do. Our headquarters and regional offices will continue to play an important role.

But to achieve the impact we want, we have no choice but to strengthen and empower our country offices.'

Malaria and climate change

The evidence continues to point to a warming of the Earth. Professor Bill Brieger looks at the initial likely winners and losers of the malaria transmission map across Africa

Climate itself is a basic determinant of the distribution of malaria in the world. As the US Centers for Disease Control and Prevention (CDC) explains, 'Climate can influence all three components of the life cycle. It is thus a key determinant in the geographic distribution and the seasonality of malaria.'[1] Thus for anopheles mosquitoes there needs to be adequate rainfall to create stable breeding sites that will neither dry up nor be washed away for a 9-12 day period. Then survival of the malaria parasite within the adult mosquito requires ambient temperatures of 15°C and higher for *P. vivax* and 20C and higher for *P. falciparum*. Finally CDC notes that higher temperatures may encourage humans to sleep outdoors and/or unprotected due to comfort or work out in the fields. Even if malaria has been eliminated from an area, if these rainfall, humidity and temperature conditions persist, there is danger that the disease can be reintroduced.

Scientists and public health officials have noticed for a number of years, as Olsen and colleagues point out that, 'Climate changes are altering patterns of temperature and precipitation, potentially affecting regions of malaria transmission.'[2] The World Health Organization posits that, 'Between 2030 and 2050, climate change is expected to cause approximately 250,000 additional deaths per year, from malnutrition, malaria, diarrhoea and heat stress.'[3] Furthermore WHO points out that with excess rainfall in some areas as a result of change, 'Floods contaminate freshwater supplies, heighten the risk of water-borne diseases, and create breeding grounds for disease-carrying insects such as mosquitoes.'

Ngarakana-Gwasira and co-researchers developed a transmission model as a framework for understanding the impact of temperature and rainfall on malaria dynamics.[4] They identified areas where there could be a dying out of malaria due to drying conditions, such as in southern Africa, and an increase in malaria in area of higher elevation as temperatures increase. These findings not only compel us to monitor climate conditions and parasite levels, but to use the information to plan appropriate interventions that change with realities on the ground.

Likewise, modeling efforts by Leedale and co-researchers found that, 'dynamical and spatially explicit

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Elongated dry seasons threaten both existence and livelihood

epidemiological malaria models response to future climate change is similar in terms of sign and spatial distribution, with malaria transmission moving to higher altitudes in the East African Community (EAC) region, while transmission reduces in lowland, marginal transmission zones such as South Sudan.'[5] Their climate model ensemble generally projects warmer and wetter conditions over EAC.

Land-use patterns not only drive climate change, but in combination with climate change can alter the potential for malaria transmission in an environment. Overgrazing on one area might lead to desertification while deforestation for increasing agricultural land may lead to greater malaria transmission. Tompkins and Caporaso contrast the Sahel and Mozambique.[6] Increases in temperature in areas of land use conversion to farmland may result is a more intense transmission and longer transmission seasons in places like Mozambique. In contrast warming observed and modeled in the Sahel region reduces malaria risk as temperatures are already above the 25-30°C threshold at which transmission peaks.

Variations in changing malaria transmission across regions may be expected. What Imai *et al*. found in Papua New Guinea is that important variations in response to climate change occur within countries.[7] They suggest location-specific approaches to investigations and surveillance and also public health interventions. This is in keeping with the recently updated WHO guidance on malaria elimination that stresses stratification of malaria burden and transmission within countries.[8]

These strata of higher or lower transmission may change, contract or expand with climate change. According to Escobar and colleagues, vectors of different diseases will respond differently to climate changes.[9] Their analysis in Ecuador revealed patterns that suggest the 'vectors of arboviruses and leishmaniasis will experience geographic range reductions by 2100 under future climate conditions, while a malaria vector, *An. Darling*, was predicted to increase in the geographic range.

Currently normal climate variations in the Pacific and Indian Oceans affect malaria transmission in eastern and southern Africa. As climate change affects and intensifies these normal patterns, the effect in Africa will also be felt. Mabaso and co-researchers evaluated the association between annual malaria incidence and El Niño Southern Oscillation (ENSO) five countries in

Southern Africa from 1988 to 1999. Below normal incidence of malaria synchronised with a negative El Niño and above normal incidence with a positive La Niña, which lead to dry and wet weather conditions, respectively.[10]

With extreme precipitation comes flooding. Boyce *et al*. 'observed that extreme flooding resulted in an increase of approximately 30% in the risk of an individual having a positive result of a malaria diagnostic

test in the post-flood period in villages bordering a flood-affected river, compared with villages farther from a river,' in the highlands of Uganda.[11] This too could have a relationship with the El Niño southern oscillation.

As noted above, a changing climate, even a warming climate, does not directly translate into greater malaria transmission. Lafferty and Mordecai explain that we need a need 'a greater appreciation for the economic and environmental factors driving infectious diseases,' as these have their own impact on transmission.[12] Climate change effects occur in parallel to 'changes such as land conversion, urbanisation, species assemblages, host movement, and demography.' This wider ecological understanding is needed to 'predict which diseases are most likely to emerge where, so that public health agencies can best direct limited disease control resources.'

As the WHO framework for malaria elimination stresses, 'Most countries have diverse transmission intensity, and factors such as ecology, immunity, vector behaviour, social factors and health system characteristics influence both the diversity of transmission and the effectiveness of tools, intervention packages and strategies in each locality.'[8] The Framework goes further to encourage strategic planning and interventions appropriate for the diverse settings or strata within a country. What climate change implies is that the nature of malaria transmission in these strata will change as temperature, rainfall, humidity and human response change. Countries not only need to adapt malaria activities to existing strata, but also be alert to changes in transmission and thus changes needed in strategies.

Increased or decreased vector control activities would be one example of changes that are needed in response to climate, vector habitat and transmission changes. 'The receptivity of an area (to vector control interventions) is not static but is affected by determinants such as environmental and climate factors.' Case detection will become even more crucial as transmission drops and the success of elimination programs depends on identifying, tracing and responding to remaining cases promptly and accurately.

The landscape for malaria control and elimination is shifting in part because of the success of interventions since the dawn of Roll Back Malaria in 1998. As we have shown here, there may also be shifts due to climate change. Of great concern is the shifts that expose new and more vulnerable populations, such as those in the East Africa highlands to the threat of malaria. National Malaria Programmes need strong surveillance efforts that monitor disease, vectors and climate, and be ready to respond.

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Lesotho to upgrade national laboratories to accelerate fight against TB

The management of TB requires precise diagnosis which in itself requires a hazard-free environment. Lesotho is meeting the challenge

TB service delivery in the Kingdom of Lesotho is impacted by long delays between sample collection and receiving test results, especially in the rural areas and townships where TB laboratories are not operating optimally. In extreme cases, this process can take as long as three months and there is a backlog of over 900 TB samples. This leads to delayed commencement of treatment. The Ministry of Health has earmarked the renovation of two TB laboratories – National TB Reference Laboratory and Leribe TB Laboratory – to address these problems and bottlenecks. In addition, upgrades are planned at three Correctional Service Facilities with the goal of creating TB isolation wings to reduce exposure to TB infection and transmission among prison inmates.

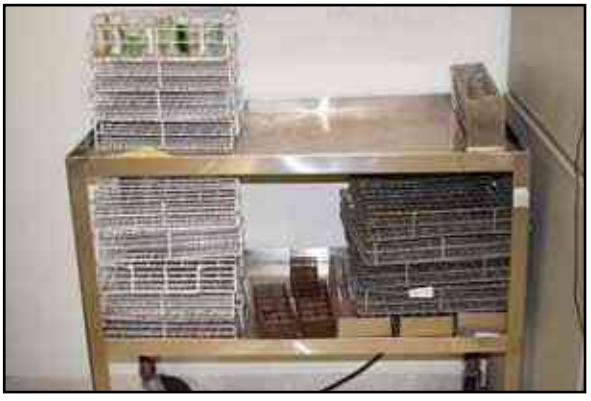
The upgrades are aimed at improving the delivery of TB services to ensure they meet occupational health and safety, and infection control standards. The scope of the planned renovations of the laboratories is informed by the World Health Organization comprehensive assessment, together with one conducted by the Africa Centre for Disease Control. During a joint project support mission to the country conducted by the World Bank, NEPAD Agency and East Central and Southern Africa Health Community, the Deputy Principle Secretary in the Ministry of Health in Lesotho, Palesa Mokete confirmed that an Engineer has since been employed under the Southern Africa Tuberculosis and Health Systems Support (SATBHSS) project to oversee and supervise these works from a technical perspective with support from other government units.

'We have a backlog of TB samples at the National TB Reference Laboratory and renovating this laboratory will help to reduce these numbers,' Ms. Mokete said.

The current state of the TB laboratories poses many hazards to service providers and to the management of specimens according to internationally accepted standards. The Permanent Secretary at the Ministry of Labour and Employment, Maseithati Mabeleng, emphasised that her Ministry will take responsibility for implementing the Occupational Safety and Health (OSH) component on the project to accelerate progress.

'The SATBHSS project comes at the right time and will answer most of the questions that have hindered TB screening, as well as access to social benefits for the ex-miners who once worked in South Africa and left without accessing their benefits', Mrs Mabeleng said.

Through the SATBHSS project, the national OSH profile in Lesotho will be updated. The Permanent Secretary at the Ministry of Mining, Soaile Mochaba, acknowledged the work being done under the SATBHSS project through a multi-sectoral approach involving different ministries. He reminded everyone that the biggest driver of TB and occupational lung diseases in Lesotho is mining, so the mining companies must be stakeholders in addressing the scourge of TB.



Storage of samples in the laboratories will be improved

'This project is creating synergies that will ensure our Ministries work collaboratively to implement multi-sectoral approaches to kick out TB and occupational lung diseases in Lesotho', Mochaba said.

The renovations will involve removing and replacing the current roof covering with more economical and maintenance-free aluminium sisalation membrane to prevent rain water penetration and formation of water drops caused by water vapour, especially during the rainy season. In addition, the damaged doors to the secure areas will be replaced by new ones with a heated viewing window. The new doors to the Ante Rooms will be replaced by aluminium ones that interlock with electromagnetic latches to ensure that when one door is open the other must be closed.

Furthermore, the existing wooden pass boxes will be replaced with heavy-duty metal pass boxes in GL powder coating. The cracked walls will be reinforced and broken water pipes replaced to ensure they are sealed, safeguarding specimens in the laboratory and preventing accidents.

The upgraded laboratories will aim to attain certification level with international accepted standards for TB laboratories and meet standards for occupational health and safety. Revamping the will help in help the laboratories to operate optimally and strengthen efforts to end TB by 2030 in Africa.

This article was written by a member of the NEPAD communications team

Seasonal malaria chemoprevention: how to sustain the impact in Africa's sub-Sahel region?

Over recent years, countries in the sub-Sahel of Africa have witnessed the life-saving impact of SMC. Medicines for Malaria Venture (MMV) discusses the challenges that remain to widespread implementation of this strategy

In some regions of the sub-Sahel of Africa, Seasonal Malaria Chemoprevention (SMC) has reduced malaria cases in children under 5 years by up to 65% during the transmission season.[1] As a result of this impressive impact and with support from several organisations, implementation of SMC by the National Malaria Control Programmes in 11[2] of 15 eligible countries plus Togo (which was not initially identified as an eligible country but has implemented) has expanded year-on-year since 2014. The next step is to explore how to reach almost all the estimated 25 million children eligible for the intervention in all 15 eligible countries in the sub-Sahel region.[3]

SMC, recommended by the World Health Organization (WHO) since 2012, involves the intermittent, monthly, dosing of the antimalarial drug combination of sulfadoxine-pyrimethamine plus amodiaquine (SPAQ) during the rainy season. The dosing regimen enables therapeutic drug concentrations to be maintained in the blood, thus providing protection from malaria throughout the period of greatest risk. SMC is recommended for children below 5 years of age.

The regions considered eligible for the intervention are those in Africa where these drugs still remain efficacious and where more than 60% of malaria cases occur in just 4 months of the year, during the rainy season. At present, these criteria restrict the intervention to specific regions in some 15 countries in the sub-Sahel, namely Benin, Burkina Faso, Cameroon, Chad, The Gambia, Ghana, Guinea, Guinea Bissau, Mali, Mauritania, Niger, Nigeria, Senegal, Sierra Leone and Sudan as well as Togo. So far, Benin, Mauritania, Sierra Leone and Sudan have not yet implemented SMC.[4]

Moving towards wide-scale implementation: what's the progress?

SMC is gaining traction as countries experience the benefit first-hand. Since 2014, implementation in the aforementioned 12 countries has been gradual for logistical reasons as well as owing to insufficient funding.

The 12 countries have integrated SMC into the package of interventions provided by community health workers and volunteers, and community leaders have been heavily involved in supporting local information campaigns. This resulted in SMC coverage beyond 85% of target children in all countries. In some areas of Guinea, coverage reached up to 100% in 2015 during the fourth round of distribution.[6] Also, from one year to the next, mothers and caregivers are noticing a reduction in malaria morbidity in their children.

'All my children have had malaria so I am very happy to have SMC now. Since my son started taking this medication, he has not been sick. This is the first year he has not had malaria.'

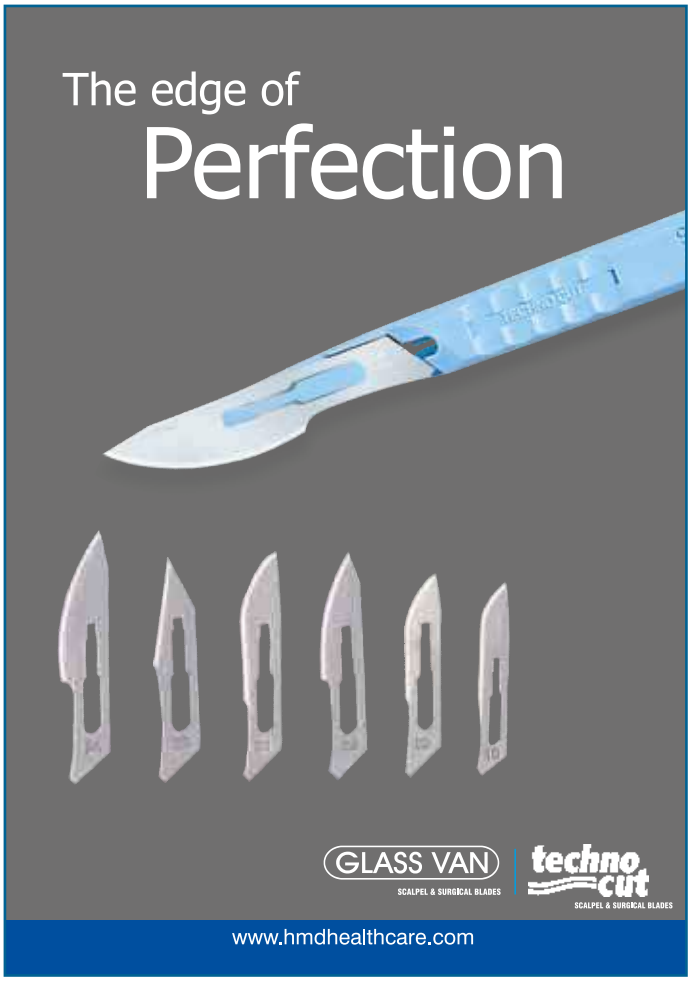
Salamatu, mother, Sokoto, Nigeria[7]

From 2015 to 2017, the ACCESS-SMC project funded by UNITAID and led by Malaria Consortium and Catholic Relief Services has been critical in scaling-up SMC implementation in seven countries: Burkina Faso, Chad, Guinea, Niger, Nigeria, Mali and The Gambia. The project reported a 24–65% decrease in malaria case incidence during the transmission season in SMC areas in children under 5 years of age. With the reduction in malaria cases in the 0-5 year age group, the burden of malaria is being pushed up the age ladder for unprotected children, as those in the 5-10 year age group are still falling sick at the same rate as before. This relative increase in malaria cases in the 5-10 year age group led Senegal to extend the intervention to this older age group in 2014, and Mali to start piloting SMC in older children in two districts as of 2016.

In line with the expansion in implementation of SMC, a concomitant increase in production and distribution of SPAQ has occurred: from a distribution of 9 million treatments in 2015 to more than 60 million treatments in 2016. The formulation, too, has evolved. At the beginning of the campaign only a hard tablet was available, obliging health workers and mothers to crush the tablets and mix them with sugar before administration to children. In 2016, dispersible, child-friendly formulations of both SP and AQ were made available by Guilin Pharma, a member of Fosun Pharma. This has helped improve convenience of the treatment and, thus, compliance. By 2017, just 3% of total country orders were for hard tablets,[8] confirming an almost complete switch to the child-friendly formulation.

In 2014, when SMC was launched, the active pharmaceutical ingredients (APIs) for sulfadoxine and pyri-

By Dr André-Marie Tchouatieu, Associate Director, Access & Product Management, and Elizabeth Poll, Communications Manager, MMV



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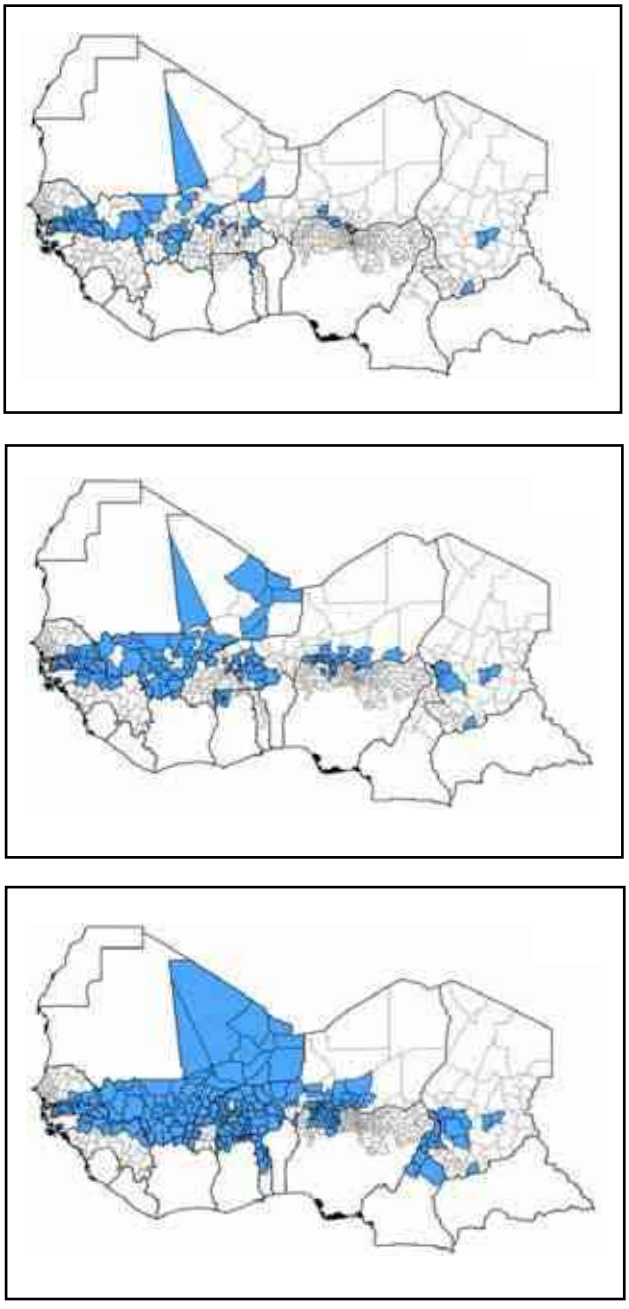

Expansion of SMC implementation (marked in blue) across the Sahel region from 2014 (top) to 2016 (bottom)[5]

methamine were not available on the WHO prequalification list. At the time, SP was only recommended for intermittent preventive treatment in pregnancy, which was not widely adopted (the coverage rate for IPTp in 2014 was estimated at 22–24%).[9] The implementation of SMC has, however, increased demand for SP, reviving the market and leading to the WHO prequalification of two sources of sulfadoxine API and one of pyrimethamine API in 2017.

Remaining challenges to widespread implementation and possible solutions

Respecting eligibility criteria: With the uptake and success of SMC, the biggest challenge countries face is ensuring sufficient funds to sustain the intervention where it has already been implemented. With success, comes the risk of over-implementation; that is, expanding SMC implementation to areas and age groups beyond WHO recommendations. Expanding to new areas/districts should ideally only be considered once the requirements for existing implementing areas have been met.

Sustained support: The ACCESS-SMC project ran from 2015 to 2017, providing both technical and financial support to SMC programs in seven countries. Anticipating the end of the project and the financial gap it would leave, countries eligible for both SMC and Global Fund grants have added requests to support the intervention to their Global Fund proposals and concept notes. New funders have also entered the malaria arena, like the Islamic Development Bank in Cameroon, and countries like Mali and Ghana have secured their own government funding to fill anticipated shortfalls from external donors. The US President's Malaria Initiative (PMI) has been supporting malaria programmes for several years in Senegal and Mali, including SMC, and has recently integrated new countries such as Burkina Faso, Cameroon and Niger. Most of these solutions are however short-term and will need to be sustained and expanded to ensure SMC can continue to be implemented.

Cost and resources: In 2016, the average cost of providing four cycles of SMC was US $3.55 per child, lower than the 2015 estimate of US $4.27.[10] However, SMC is increasing the burden on the health workers who are already in high demand. This could in-part be addressed by exploiting synergies within the local health system e.g. by coupling SMC with other public health interventions, such as nutrition supplementation distribution or vaccine administration campaigns. Such an approach would decrease the work load on the health workers and potentially further optimise the cost of the intervention.

Safety monitoring: SMC is a relatively new drug intervention; as such its scale-up should be accompanied by robust safety monitoring. The ACCESS-SMC project included a safety monitoring component to detect and report adverse reactions related to SMC drugs with an emphasis on serious reactions. The aim was to define the safety profile of SMC medicines and strengthen or support pharmacovigilance systems in countries. The approach was to take pharmacovigilance activities for SMC as the 'building and training ground' for overall pharmacovigilance systems with the goal of ultimately strengthening the country's ability to introduce other new products and strategies. These efforts have achieved good results: in one example, Chad became a part of the WHO Programme for International Drug Monitoring.[11] These efforts to build and/or strengthen pharmacovigilance systems will, however, need to be sustained.

Resistance monitoring: Routine monitoring for signs of decreasing efficacy is an important long-term consideration to accompany widespread use of SPAQ in the Sahel region. SP resistance is caused by mutation on two genes, the dihydrofolate reductase (Pfdhfr) and the dihydropteroate synthetase (Pfdhps). Mutations in the *Plasmodium falciparum* genes pfcrt and pfmdr1 are selected by amodiaquine treatment in Africa.[12] Continued use of SMC on a massive scale year-over-year will put increasing drug pressure on SPAQ throughout the Sahel region and accelerate the emergence of greater drug resistance to this chemoprevention.

The risk of rebound after cessation of SMC: Children between the ages of 3 months and 60 months who routinely receive SMC may benefit from years of protection against malaria. However, their reduced exposure to malaria may have a downside: the failure to develop strong immunological responses to malaria infection which may make them vulnerable again once they are no longer eligible for SMC.[13] This is one of the reasons some countries, for example Senegal, are choosing to implement SMC in older age groups.

Supply chain management: Several cases of late or partial delivery of SMC drugs are still being noted. Early planning by countries and local implementers as well as timely ordering of the commodities will help to improve the supply chain, which is also reliant on early commitment from funding partners. Today, there is only one WHO prequalified manufacturer of SPAQ (both tablet and child-friendly formulations). A diversified manufacturer base could help diminish the risk of disruptions in global SMC supply lines – a negative phenomenon which did in fact occur in 2015 after API sources for SPAQ were disrupted. To help address this, MMV is working with S Kant to achieve WHO prequalification of a second child-friendly formulation of SPAQ.

Migrant populations: Another challenge is the migratory nature of some populations in SMC eligible areas, which can negatively impact coverage rates. To address this challenge, the West African Health Organization (WAHO) is leading a cross-border collaboration to ensure parallel implementation of SMC across all regions.

MMV's role and future plans

MMV's involvement in SMC began in 2013 with the development of a tool kit to support SMC implementation. As a member of the UNITAID-funded ACCESS-SMC project led by Malaria Consortium since 2014, MMV has subsequently designed an online forecasting platform, which provides partners with country information on the number of children targeted by district and therefore the number of treatments needed for the subsequent 3 years. This information will help stakeholders to plan and deliver SMC on a timely basis. The tool also supports critical production planning activities for manufacturers by providing aggregated demand across all SMC countries. Recently, the tool has been expanded to enable access by other SMC stakeholders, enhancing transparency and facilitating collaboration across the broader community of SMC-eligible countries.

As an R&D-driven product development partnership, MMV also recognizes that it has a role to play in developing replacement medicines should drug resistance undermine current standards of care. Given the longer-term risks of resistance to SPAQ described above, MMV is considering which existing drugs might be used in a new combination as an alternative to SPAQ. Both components of a new combination should have a long half-life, an excellent safety profile, and ideally no history of drug resistance in sub-Saharan Africa. Although such an alternative should have a slow onset of action and would not be reliant on an artemisinin derivative, it would need to demonstrate 90% parasite clearance at day 7. Based on this profile, MMV aims to identify a potential alternative combination for SMC by the end of 2018. The combination would then need to undergo efficacy studies in SMC settings.

Conclusion

SMC is a highly-cost-effective, widely-adopted tool that is providing significant protection for young children in select regions of Africa. However, it remains a relatively new and time-bound intervention, requiring strong planning, monitoring and evaluation. The implementation campaign can be very time consuming for health care personnel at community level, substantially increasing their work load. The malaria community is coming together to address these and other challenges to SMC's widespread implementation. Furthermore, with the success of SMC in children, opportunities to consider its wider use across whole communities could make SMC relevant for the malaria elimination agenda. For now, the key focus for the SMC community, particularly following the completion of the ACCESS-SMC project in 2017, is to sustain funding and programmatic support so that SMC might reach every one of the 25 million children eligible for this life-saving intervention in Africa's sub-Sahel region.

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Difficult policy decisions needed to overcome the double disease burden

Africa faces some stark policy options if it is to deliver a demographic dividend to its people. Three senior authors put the case for change

There is no doubt: Africa will dominate global population dynamics in the 21st century. While public attention has long focused on Asia as a fast-growing and prospering market with currently 4.5 billion inhabitants, today's one billion sub-Saharan Africans have significantly outpaced Asia in terms of population growth (2.6% vs. 1.1% in 2016, respectively).

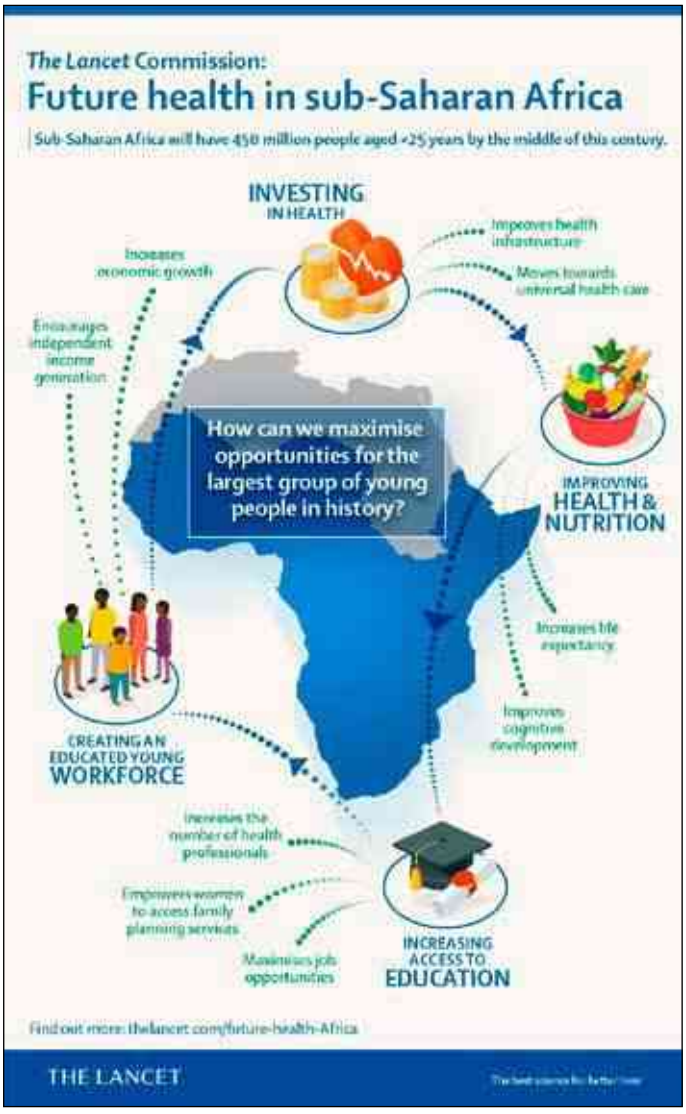
The main reason for this ongoing population growth in sub-Saharan Africa (SSA) is a sharp decline in infant and child mortality whilst at the same time, continually high birth rates over the last few decades (the fertility rate per woman was 5.1 in 2013 compared to 6.7 in 1970, while infant mortality declined rapidly from 138 deaths per thousand births in 1970 to 67 in 2013). Today, one billion people or 16% of the world population live in SSA. By 2050, this number will double and in 2100, 3.9 billion people or 39% of the world's population could live in the region. This is the official forecast according to the Medium variant of the 2015 United Nations Population Projections.

A key condition today to fulfilling this demographic dividend (DD) is the formulation of policies that will help Africa to replicate the conditions that enabled East Asian countries to prosper during the period covering the early 1960s to the 1990s. The DD is defined as an accelerated economic growth triggered by the decline in a country's birth and death rates and the relative increase in working-age adults. However, to open this demographic window of opportunity, public policies will in particular need to manage a rapid and significant decline in fertility in order to reduce the number of young dependents.

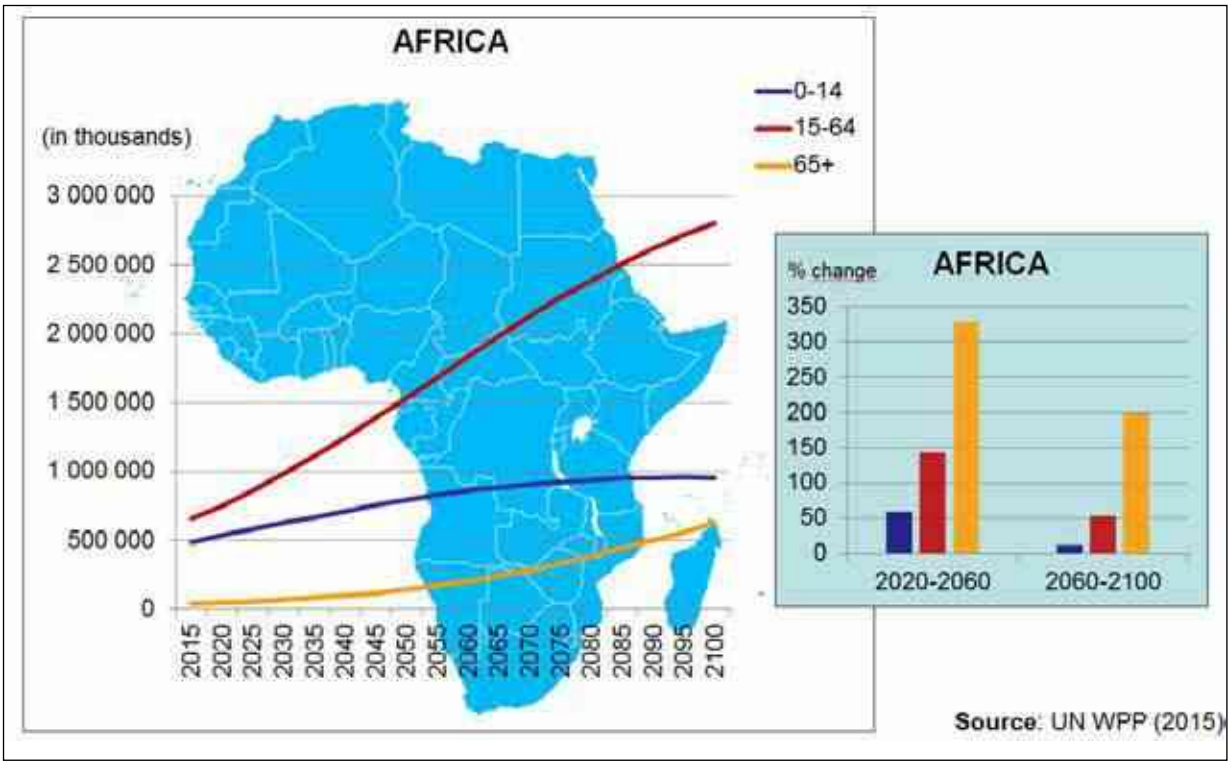
In addition, other topics are critical to capture this one-time opportunity in a sustainable manner:

Africans urgently need jobs. There will be no demographic dividend without new jobs. According to the International Monetary Fund (IMF), 18 million new jobs are needed every year till 2050. For just one year, this is equivalent to jobs for the entire population of the Netherlands. From now until 2050, the total number of new jobs required are almost equivalent to the entire European population.

Africa needs continued health investment and improvement. The window of opportunity for a demographic dividend only appears when fertility declines significantly and rapidly. This depends on further improvements of women's and children's rights and health outcomes. Making sure that women meet their reproductive health needs is a key priority. According to UNFPA, 'countries with the greatest demographic opportunity for development are those entering a period in which the working-age population has good health,



This piece is authored by Thomas Zeltner, Swiss Academies of Arts and Sciences; Thomas Cueni, Director General, International Federation of Pharmaceutical Manufacturers & Associations (IFPMA); Konji Sebati, CEO, Innovative Pharmaceutical Association of South Africa (IPASA).



Population Growth in Africa 2015-2100 by Age Cohorts (World Demographic & Ageing Forum, 2016)

quality education, decent employment and a lower proportion of young dependents. Smaller numbers of children per household generally lead to larger investments per child, more freedom for women to enter the formal workforce and more household savings for old age. When this happens, the national economic payoff can be substantial', and the demographic dividend delivers its potential.

It is clear that the demographic dividend will only become a reality if African countries **invest in the health of their populations**. Many countries have very successfully addressed the challenge of infectious diseases. An estimated three million children under age five have been saved from malaria and the incidence of new HIV cases in Sub Saharan Africa has fallen by more than half between 2001 and 2012. The next challenge is the rising epidemic of non-communicable diseases that also significantly affects this part of the world. It is too early to predict whether the success in the infectious disease area will repeat itself in the domain of non-communicable diseases. There are many obstacles to overcome. The countries of SSA have to integrate the policies to fight infectious diseases with those on NCDs, and to align the funding into one to avoid competition in resource allocation between the two areas. They need to develop integrated strategies that begin in the primary health care sector and finally, they need to define strategies on how to engage constructively with the private sector. There is much to consider.

Universal and equal access to health care is an essential global challenge for the wellbeing of the world's population and therefore requires the appropriate investment. The Lancet recently launched 'The path to longer and healthier lives for all Africans by 2030: the Lancet Commission on the future of health in sub-Saharan Africa'.[1] The Commission highlights the importance of advocating an approach based on **people-centred health systems** which can be adapted to countries' specific needs. Better health will not only benefit countries' populations directly – it will also act as a catalyst, enabling the successful pursuit of other development agendas, as summarised in the Sustainable Development Goals (SDGs). As recommended in the Lancet article, a systemic and holistic approach is required, as 'a fragmented health agenda will deliver some results but will not succeed in strengthening health service delivery and public health systems, and will not address the determinants of health'. Broad partnerships beyond the medical and health community are essential to move the health agenda forward.

Failure is not an option. A bad outcome would challenge both Africa and the global community. Not succeeding in capturing a demographic dividend in Africa would lead to millions of people living in poverty and in slums. It would result in a restless young population and facilitate human suffering and social disruption that could spill over well beyond Africa. The implications for the globe as a whole must be considered, as today's interconnected world shows that the issues and challenges that one continent faces will not be limited solely to one geographical area.

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Ebola vaccine trials: the role of eHealth

The Sierra Leone Trial to Introduce a Vaccine Against Ebola (STRIVE) enabled CDC to coordinate the activities of several hundred health staff, despite the terribly difficult circumstances

Since the height of the 2014-2016 West African Ebola outbreak and response, eHealth Africa (eHA) has worked with West African Ministries of Health (MOHs) to rigorously improve emergency management operations, electronic disease reporting systems, and laboratory and diagnostic systems. eHA's progress in Sierra Leone has gone a step further and strengthened the global Ebola research base through managing clinical trials and building partnerships with donors and local institutions to strengthen local healthcare capacity.

Healthcare workers and frontline workers are at an elevated risk for contracting Ebola during an Ebola outbreak because their work involves handling infectious blood and secretions. These high-risk occupations include doctors and nurses, and expand to include burial workers, ambulance teams, health facility staff, surveillance teams, and others working on the frontline.

During the course of the 2014-2016 outbreak, there were over 850 confirmed health worker infections reported across Guinea, Liberia, and Sierra Leone, including over 500 reported deaths. High infection rates are contributed to by the Sierra Leonean healthcare context including challenges with following infection prevention control protocols and insufficient amounts of appropriate personal protective equipment.

There were no Food and Drug Administration of the United States (FDA) approved vaccines or medicines available to prevent or treat Ebola prior to the West African Ebola outbreak. Thus, a clinical trial was needed to both test Ebola vaccines and distribute effective vaccines to the populations most at risk. Thus, the Sierra Leone Trial to Introduce a Vaccine Against Ebola (STRIVE) expanded the safety and immune information of rVSV-ZEBOV candidate Ebola vaccine gained from previous studies into a Phase 2 and Phase 3 clinical trial. STRIVE was implemented during the Ebola epidemic to allow healthcare workers to both have access to this unlicensed vaccine and also to serve as a mechanism to monitor those vaccinated for side effects.

Through STRIVE, eHA and partners enrolled and vaccinated over 8,000 healthcare workers and frontline workers against Ebola in Sierra Leone. In order to accomplish the feat, it established a nation-wide team of logisticians, district officers, call center staff, medical personnel and project management staff. eHA served as the Center for Disease Control and Prevention's (CDC) major contracted partner in executing STRIVE enabling it and leveraged partners, to subcontract clinical activities and supervision to the Sierra Leone College of Medicine and Allied Health Sciences (COMAHS). COMAHS provided over 350 clinical staff for the trial.

eHA served as the operational backbone of the trial, overseeing the logistics of the trial and supplying eight vaccination sites with trained staff. STRIVE worked to establish a national supply chain of the Ebola vaccine, and its extensive cold chain support extended to the most remote of the eight vaccination sites.

eHA adapted software and digital tools developed for the outbreak to the needs of STRIVE, allowing near real-time monitoring of participants' medical experience following vaccinations. This included building a network of public and private partnerships to create a national medical insurance scheme for participants. This scheme was linked to the 711 hotline, an independent call center open 24-hours per day staffed by eHA for STRIVE participants. Additional digital tools created included the establishment of an online patient registration tool with mobile payment services.

STRIVE continued through August of 2017 in order to conduct follow-up for it's over 8,000 vaccine trial participants. This follow-up included tracking adverse events and the presence of Ebola and treating any serious adverse events and acute medical conditions.

Ultimately, STRIVE's success was measured by eHA's ability to enroll, vaccinate and monitor enough participants for the evidence to contribute to licensure of a vaccine against Ebola. This trial's timely and strategic execution meant that a large portion the Sierra Leonean workforce most at risk for contracting Ebola received a vaccination. eHA is proud of their completion of Sierra Leone's largest clinical trial, especially because it was executed during both an emergency response and a national state of emergency.

Taylor M. Snyder, MPH serves as eHealth Africa's Senior Technical Advisor. If you have any questions about eHealth Africa's work building stronger health systems through implementing data-driven solutions across West Africa, contact her at taylor@mihealthconsulting.com.

Why the ongoing harmonisation of regulation of medicines in Africa should be patient-centric

Kawaldip Sehmi argues the case for the patients' voice to be heard

Cases of expired drugs quite often go unreported not only because of limited awareness and enforcement of patients' rights but also due to inadequate access to vital information, such as medicine side effects. Access to quality drugs remains a particular challenge as costs remain at exorbitant levels.

Across Africa, media reports frequently highlight issues, such as expired drugs that are reported to have been imported by governments or donations. In some countries, National Drug Authorities have limited capacity to test drugs due to inadequate laboratory analysis facilities, with most countries relying on certificates of authorisation to manufacture drugs that run the risk of potentially being forged.

It is against this backdrop that the creation of the African Medicines Agency (AMA) in 2018 – a process spearheaded by the New Partnership for Africa's Development (NEPAD) under the African Union (AU) and the World Health Organization (WHO) – is a timely development.

Optimism is high as the initiative aims to strengthen patient access to safe, efficacious and quality assured medicines across Africa by pursuing stronger regulatory harmonisation amongst the AU member states.

At the International Alliance of Patients' Organizations (IAPO), as strong advocate for patient-centred healthcare globally, we are actively campaigning to ensure that AMA engages patients as key partners. We believe patient engagement in regulatory harmonisation must take place as early as possible and be nurtured over time.

The question of how to ensure that the future AMA is truly patient-centric was the core focus of IAPO's African Regional Meeting, held in Entebbe, Uganda, in July 2017. This was an opportunity for the community of IAPO's African patient advocates to come together and discuss how patients can engage with the African Medicines Agency.

A key outcome of the meeting was the drafting of a joint statement – the Entebbe Statement – calling for a patient-centric African Medicines Agency. The statement highlights the importance of ensuring that patients are placed at the centre of regulatory harmonisation processes for medicines in Africa.

Patient groups, therefore, have an unprecedented opportunity to be part of the conversation right from the start, and to be co-drivers in the harmonisation process, even before the birth of the AMA. Early engagement would enable patients to have a meaningful say, not only on medicines regulation, but also on the strategic direction and practical functioning of the entire harmonisation journey.

It is crucial that every patient has a real opportunity to access high-quality health services. At the same time, patients cannot truly take responsibility as equal healthcare stakeholders if they are left behind in key decision-making processes.

Patient involvement must not be seen as a concession that other stakeholders grant to patients on a discretionary basis. Rather, genuine patient involvement is a key way of empowering patients to take their share of responsibility, and become key partners, with an equal seat at the table.

Kawaldip Sehmi is the Chief Executive Officer of the International Alliance of Patients' Organisation, a global patients alliance working to have patient-centred healthcare firmly on the global health agenda.

Structure and function of red and white blood cells

Barbara J Bain

Abstract

Red cells have a major function in transport of oxygen and minor functions in regulation of local blood flow and transport of carbon dioxide. Neutrophils and monocytes are phagocytic cells that are part of the innate and also the adaptive immune response. Eosinophils have their major function in protecting against multicellular parasites, and basophils participate in this process. B cells are part of the adaptive immune response, specifically differentiating to plasma cells, which are responsible for humoral immunity. Some T cell subsets and natural killer (NK) cells mediate cellular immunity, both innate and adaptive, while other T cell subsets suppress the activity of B cells, helper T cells and cytotoxic T cells. NK cells and cytotoxic T cells are important in defence against tumours.

Keywords B cell; basophil; cytotoxic T cell; eosinophil; eryptosis; erythrocyte; haemoglobin; helper T cell; leucocyte; lymphocyte; monocyte; natural killer cell; neutrophil; oxygen transport; red cell; red cell senescence; reticulocyte; suppressor T cell; T cell; white cell

Key points

- Erythrocytes have a major function in oxygen transport, with more minor roles in transport of carbon dioxide and regulation of vasodilation
- Neutrophils and monocytes are phagocytic cells that contribute to both innate and adaptive immune responses
- Monocytes differentiate into macrophages, which function as phagocytes, antigen-presenting cells and immune modulators, and in iron storage
- Eosinophils and basophils have a role in protecting against parasitic infections
- Lymphocytes interact with neutrophils, monocytes, macrophages and dendritic cells, and have a major role in innate and adaptive immune responses

Introduction

The red cells (erythrocytes) and white cells (leucocytes) are normally produced in the bone marrow, being ultimately derived from a pluripotent haemopoietic stem cell. White cells comprise granulocytes (neutrophils, eosinophils, basophils), monocytes and lymphocytes. Note that the term 'granulocyte' should not be used as a synonym for neutrophil; it has a broader meaning.

Red cells

The human red cell can be regarded as a miracle of evolution. Once past the reticulocyte stage, it has lost not only its nucleus, but also organelles such as mitochondria, Golgi apparatus and endoplasmic reticulum with its ribosomes, and has assumed the form of a hollowed-out disc. This disciform shape provides a large surface for the exchange of oxygen. The lack of organelles means that the red cell is flexible and can easily deform to pass though capillaries and splenic sinusoids.

Haemoglobin is a metalloprotein composed of four α- or α-like and two β- or β-like globin chains, each globin chain enclosing a haem moiety. The major function of red cells is the uptake of oxygen from the lungs and its delivery to the tissues, by oxygenation of the ferrous (Fe^{++}) ions of haem. Around 98% of oxygen transport is by red cells, only 2% being transported in the plasma. The red cell has a diameter greater than that of a capillary; the need to deform and squeeze through the capillary is likely to improve transfer of oxygen from the erythrocyte to the tissues.

The red cell is also capable of transporting carbon dioxide from the periphery to the lungs, by binding carbon dioxide, as carbamate, to the N-terminal end of the α-globin chain, with its subsequent release as carbon dioxide in the lungs. However, the red cell is only responsible for transporting about 15% of the carbon dioxide, the rest being transported in the plasma. Deoxyhaemoglobin also functions to generate nitric oxide from nitrite, and can thus contribute to vasodilation in the peripheral tissues. The confining of haemoglobin within the red cell means that there is protection against the ability of oxyhaemoglobin to inactivate nitric oxide, which occurs when there is intravascular haemolysis, leading to vasoconstriction and a thrombotic tendency.

The constituent parts of the haemoglobin molecule are synthesized and assembled in erythroblasts in the bone marrow. This requires the presence of ribosomes, on which globin chains are assembled, and mitochondria, which are required for some stages of haem synthesis. The reticulocyte retains mitochondria and ribosomes. This means that haemoglobin synthesis can continue for the 1–2 days the reticulocyte spends in the circulation, and up to 10% of such synthesis occurs in these cells. The pairing of two dissimilar globin chains and the cooperativity between them are essential for the sigmoid oxygen dissociation curve, which ensures efficient uptake of oxygen in the lungs and efficient delivery in the tissues (Figure 1). The oxygen affinity of normally structured haemoglobin means that such uptake and delivery of oxygen is achieved at a red cell count/haemoglobin concentration/haematocrit that does not lead to hyperviscosity.

Other requirements must be met for the red cell to fulfil its major function — transporting oxygen. The following are

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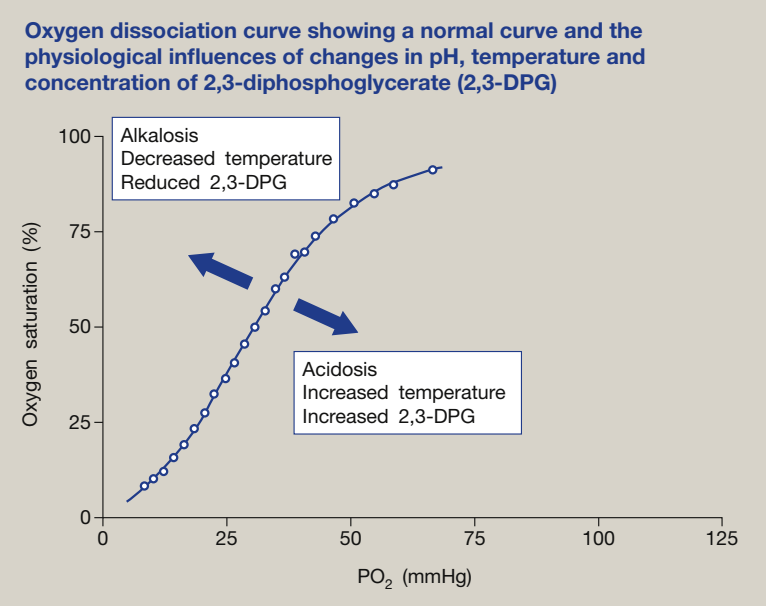

Figure 1

essential for normal function: a permeable membrane; maintenance of the disciform shape and cell flexibility; the ability to convert methaemoglobin (which is spontaneously produced and cannot transport oxygen) to haemoglobin; production of energy in the form of adenosine triphosphate and generation of a reduction potential in the form of nicotinamide adenine dinucleotide (NADH) by means of the Embden–Meyerhof pathway; generation of further reduction potential in the form of NADH phosphate (NADPH) by means of the pentose shunt; and the ability to produce 2,3-diphosphoglycerate (2,3-DPG), which interacts with the haemoglobin tetramer to reduce oxygen affinity and improve oxygen delivery to the tissues. An increased concentration of 2,3-DPG can compensate for anaemia. NADH and NADPH protect the erythrocyte from endogenous and exogenous oxidants. Relevant metabolic pathways are summarized in Figure 2.

The structure of the red cell reflects its function: a cell membrane encloses cytoplasm that has haemoglobin as the major component, with carbonic anhydrase the second most abundant protein. The membrane is composed of a lipid bilayer through which pass various proteins with diverse functions including the transport of anions, water and glucose and the binding of the lipid bilayer at various points to the underlying cytoskeleton, thus maintaining the cell shape (Figure 3). The cell membrane has other functions at the end of the erythrocyte's lifespan of about 120 days. Red cell senescence is the result of a conformational change in a membrane protein, band 3, leading to the appearance of a senescence-specific antigen recognized by autologous immunoglobulin (Ig) G, marking the cells for removal by macrophages.[1] In addition, aged red cells are also more susceptible to oxidant stress and therefore to eryptosis. In this process, there is externalization of membrane phosphatidylserine leading to binding to CD36, the phosphatidylserine receptor on macrophages, with resultant phagocytosis.[1]

Neutrophils

Polymorphonuclear neutrophils are produced in the bone marrow and circulate in the blood before migrating to the tissues, where their main functions are fulfilled. Their lifespan in the circulation is about 7–10 hours and in tissues is 1–2 days. Most neutrophils have a nucleus divided into two to five lobes separated from each other by a thin filament. A minority, referred to as band forms, have a non-lobulated nucleus in the shape of a curved band; with maturation, the nucleus of the band forms develops lobes.

The neutrophil cytoplasm contains some ribosomes, small numbers of mitochondria, glycogen and granules of various types.[2] Only the primary or azurophilic granules are visible by light microscopy. On May–Grünwald–Giemsa (MGG)-stained blood films, they are lilac. They contain myeloperoxidase, defensins, lysozyme, neutrophil elastase and cathepsin G. The secondary, specific or neutrophilic granules are visible by electron microscopy, and on MGG-stained films are responsible for the pink tinge of the cytoplasm. They contain lactoferrin, transcobalamin, collagenase, gelatinase, lysozyme and cathelicidin. Tertiary granules, also below the level of resolution of the light microscope, contain gelatinase and lysozyme. Neutrophil alkaline phosphatase is contained within secretory vesicles.

Neutrophils are part of the innate immune system. Their functions include: margination; adhesion to the endothelium; transcellular and paracellular migration through the endothelium

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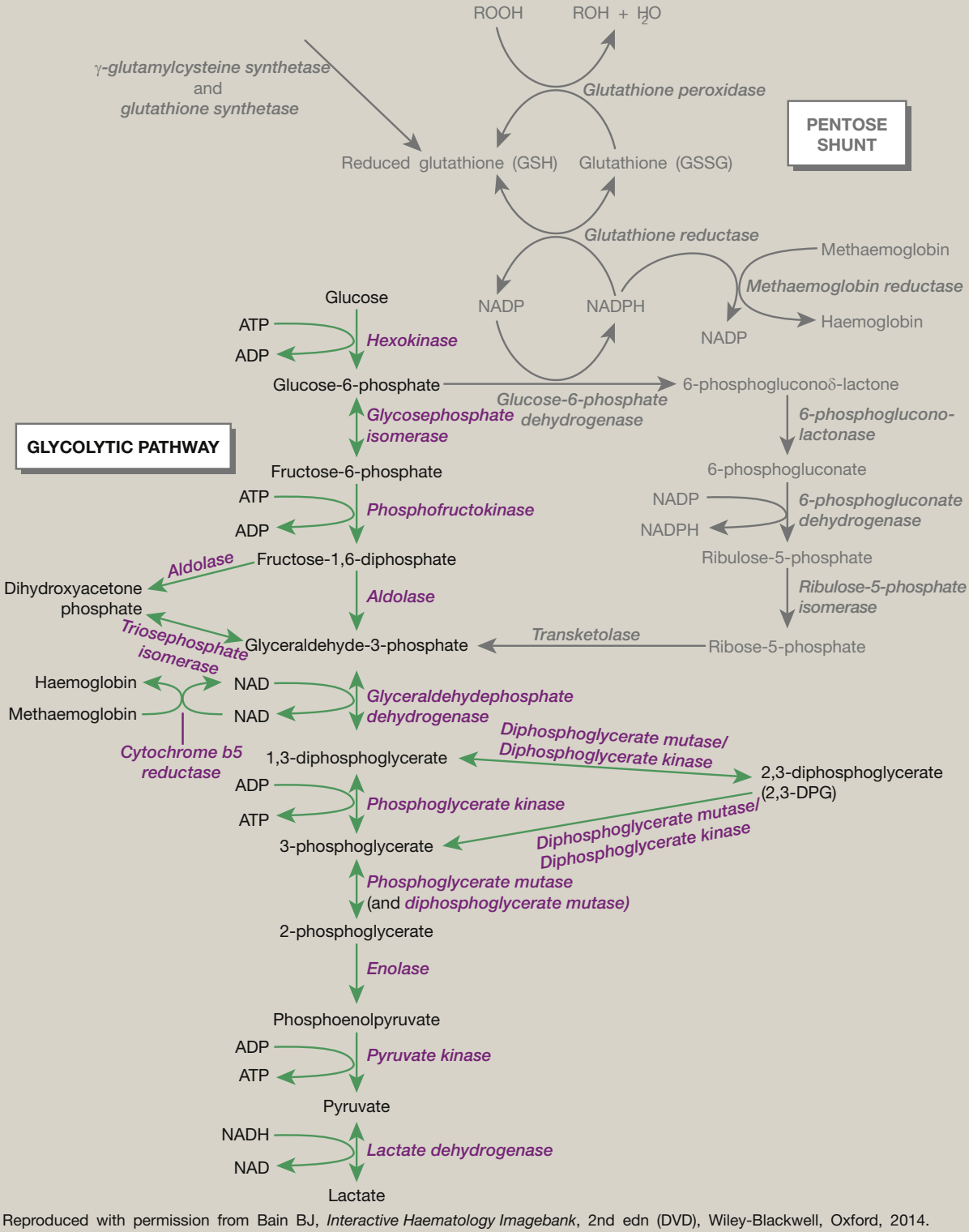
The glycolytic pathway and the pentose shunt



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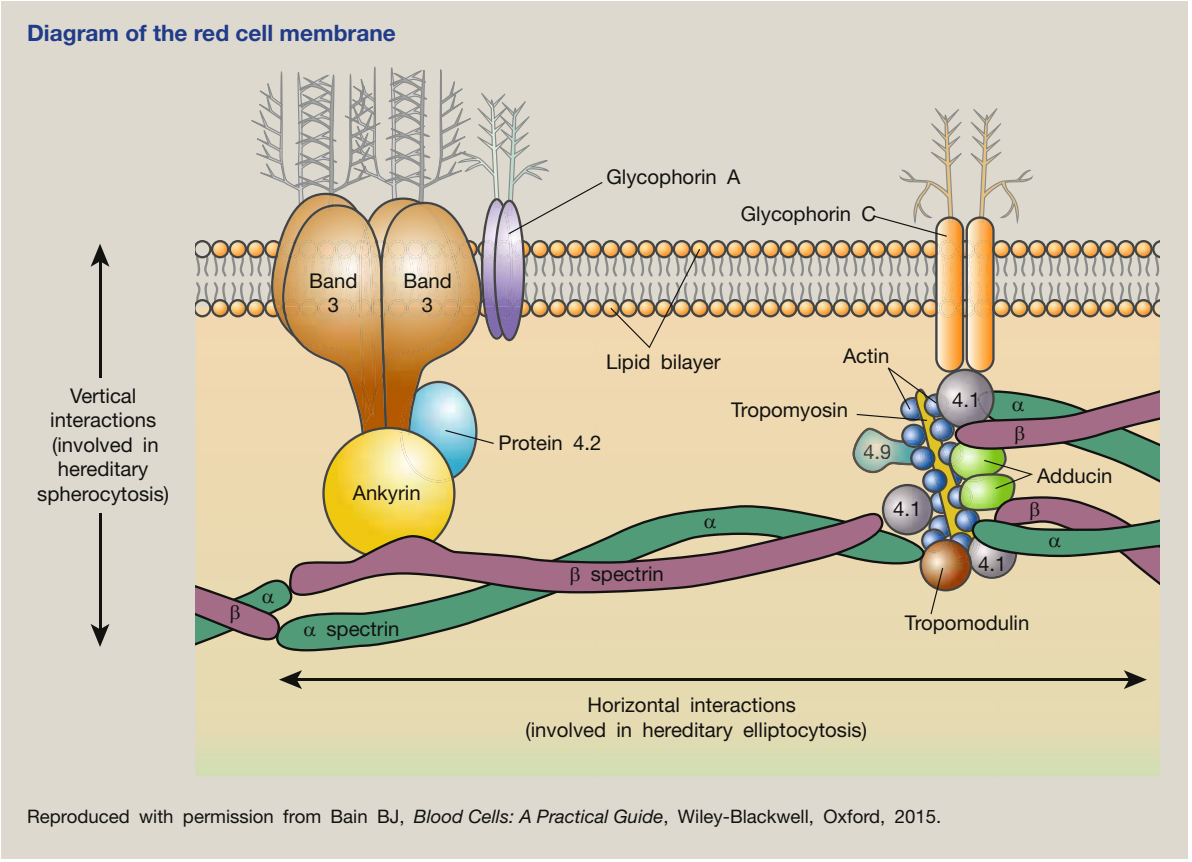

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Figure 3

(diapedesis); movement through the tissues in response to chemotactic stimuli (chemotaxis); phagocytosis, killing and digestion of microorganisms; and phagocytosis and digestion of dead cells and cellular debris (Figure 4).[3]

Margination and rolling along the endothelium is achieved by selectins on the neutrophil surface membrane. Adhesion requires adhesion molecules, which are upregulated in infection and inflammation. Chemotaxis occurs as a result of the presence of membrane receptors that can detect complement 5a and various cytokines, such as interleukin (IL)-8 and interferon-γ, allowing the neutrophil to migrate against a concentration gradient. The process of phagocytosis is enhanced when microorganisms are opsonized by complement or Ig.

Phagocytosis is followed by fusion of granules to the phagocytic vacuole (phagosome), with granule contents, including proteolytic enzymes, being emptied into the phagosome. A respiratory burst then leads to generation of hypochlorous acid plus hydrogen peroxide and other activated oxygen species within the phagosome. This, plus the action of proteolytic enzymes, leads to killing and digestion of microorganisms and digestion of other phagosome contents. Killing of microorganisms is further enhanced by generation of neutrophil extracellular traps.[4] These comprise a lattice of extracellular chromatin fibres (DNA, histones) together with proteolytic granule proteins. Their formation is triggered by reactive oxygen species. They mediate extracellular killing of microorganisms (bacteria, fungi) and can also create a physical barrier around an area of infection.

Eosinophils

Polymorphonuclear eosinophils are slightly larger than neutrophils. The nucleus is usually bilobed. Eosinophils have acidophilic granules, which are larger than those of neutrophils. On an MGG-stained film, they are orange because of their affinity for the eosin component of the stain. Occasionally, particularly in reactive eosinophilia, there are some purple proeosinophilic granules. In addition to granules, the weakly basophilic cytoplasm contains abundant glycogen particles and more numerous and larger mitochondria than are found in neutrophils; there is also some rough endoplasmic reticulum.[2] The granules have a crystalline core composed of eosinophil major basic protein surrounded by a matrix containing eosinophil cationic protein, eosinophil peroxidase, eosinophil-derived neurotoxin, plasminogen, ribonucleases, deoxyribonuclease and lipase. The eosinophil lifespan is about 1 day in the circulation and 8–12 days in the tissues.

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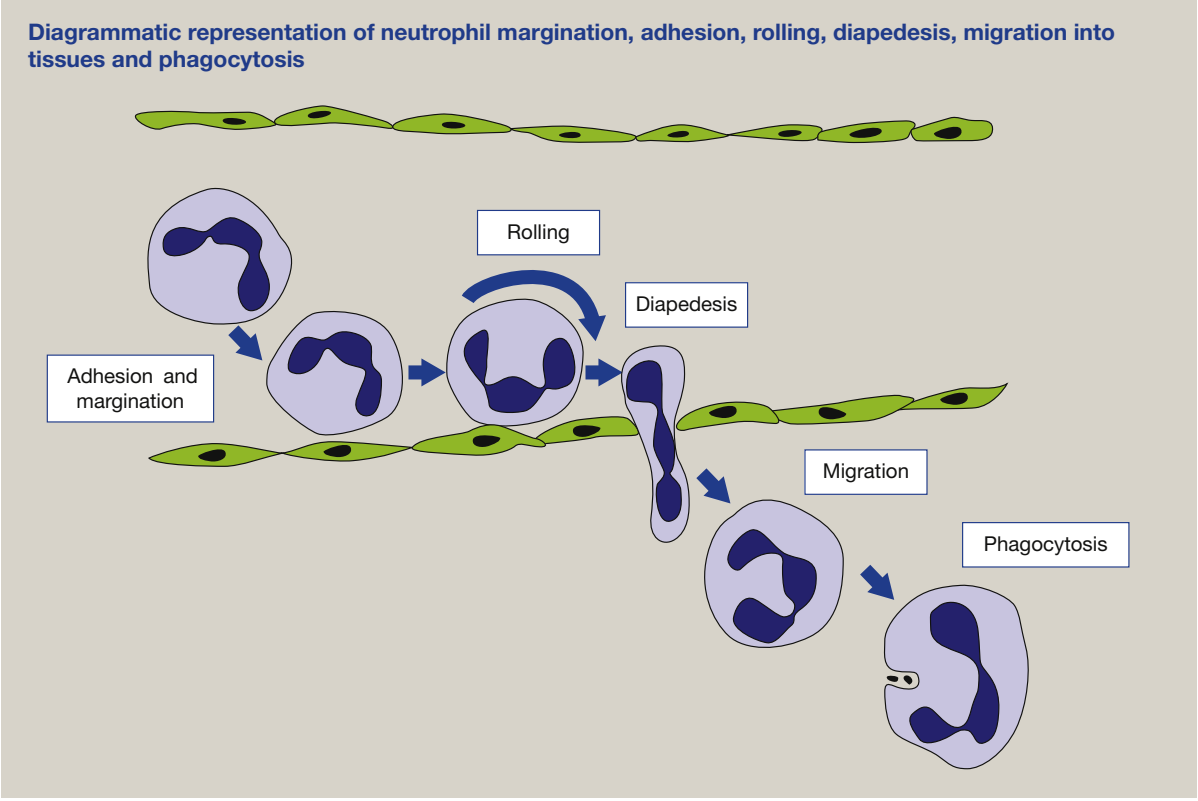

Figure 4

Eosinophils synthesize and secrete growth factors, cytokines and chemokines; they have a role in the regulation of innate and adaptive immune responses and in tissue remodelling and repair. They trigger release of histamine by basophils and mast cells, and are important in the control of infection by multicellular parasites. They are attracted to the sites of parasitic infection by chemokines such as eotaxin 1 and 2, and at such sites are activated by cytokines produced by helper T cells. They attack parasites by degranulation and peroxidase-mediated generation of reactive oxygen species. Eosinophil neurotoxin and ribonuclease have antiviral properties.

In addition to their useful functions, eosinophils are implicated in maladaptive allergic conditions. They can also cause collateral damage to normal tissues as a result of the eosinophil response to parasitic infection.

Basophils

Polymorphonuclear basophils are granulocytes which, on MGG-stained films, have large dark purple granules that almost obscure the nucleus. The nucleus is usually bilobed. Basophils survive many days in the circulation. In addition to the granules, the cytoplasm contains scattered glycogen particles, membrane whorls, Golgi apparatus, a few mitochondria and a small amount of rough endoplasmic reticulum.[2] Basophils have some phagocytic activity and degranulate when IgE binds to a specific membrane receptor. They have a role in protection against helminth infections but are also involved in allergy, anaphylaxis and chronic inflammation; they secrete histamine, serotonin, heparin, proteolytic enzymes, IL-4 and IL-13.

Monocytes

Monocytes are the largest peripheral blood cells. On MGG-stained films, they have an irregular, usually lobulated, nucleus and opaque greyish-blue cytoplasm containing fine azurophilic granules and often vacuoles. They are phagocytic cells and are part of the innate immune system. However, their functions are broader than those of neutrophils. They retain proliferative capacity and, following migration to tissues, differentiate into macrophages and other specialized cells of the reticuloendothelial system, and into dendritic cells and osteoclasts. Some cells (e.g. Kupffer cells of the liver) are fixed, while other remain mobile.

In addition to phagocytosis and killing of microorganisms (including mycobacteria, *Listeria* and fungi), monocytes are antigen-presenting cells and thus involved in lymphocyte selection and activation. They are immune modulators, secreting IL-1, IL-6, IL-12, tumour necrosis factor-α, interferon-α and interferon-β when stimulated, thus enhancing the

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Subsets and function of T cells and natural killer (NK) cells

Type of lymphocyte	Subsets	Function
CD4-positive (approximates to helper subset)	Natural regulatory T cell	Regulation of immune responses
	NK-like T cell	Anti-tumour immunity following activation by antigens
	Type 1 helper T cell	Immunity to intracellular pathogens (activation of macrophages, mediation of cytotoxicity, promotion of cellular immune responses), induce delayed hypersensitivity
	Type 2 helper T cell	Immunity to many extracellular pathogens including helminths (promote B cell proliferation and antibody secretion, induce IgE secretion, recruit eosinophils to sites of inflammation)
	Type 17 helper T cell	Immunity to extracellular bacteria and fungi (recruit and activate neutrophils, increase monocyte production); can mediate acute graft-versus-host disease
	Induced regulatory T cell	Immune tolerance (self-tolerance, tolerance of allografts), lymphocyte homeostasis, regulation of immune responses
CD8-positive (includes cytotoxic and suppressor subsets)	Cytotoxic T cells	Antigen recognition in a human leucocyte antigen class I context with resultant cytotoxicity; important in defence against viral infections and in allograft rejection
	Suppressor T cells	Suppress the activities of B cells, cytotoxic T cells and helper T cells
NK cells	NK cells (cytologically large granular lymphocytes)	Direct killing of virus-infected cells or tumour cells by cytotoxic granule contents Antibody-dependent cellular cytotoxicity Production of immunoregulatory cytokines

Table 1

inflammatory response. On ultrastructural examination, the cytoplasm contains heterogeneous granules, glycogen particles, mitochondria, an active Golgi apparatus and short lengths of endoplasmic reticulum.[2] Their intravascular lifespan is 1–3 days, while the cells into which they differentiate are long-lived.

Macrophage functions include the removal of unicellular parasites from erythrocytes, removal of Howell–Jolly bodies and other red cell inclusions, removal from the circulation of senescent red cells, phagocytosis of other senescent or dead cells, storage of iron as ferritin and haemosiderin, and supply of iron to developing erythroblasts. Macrophage activity has some adverse effects, specifically in the pathogenesis of anaemia of chronic disease.

Lymphocytes

Lymphocytes are the smallest leucocytes, approximately round with a fairly round nucleus. Most have scanty cytoplasm, but some have more plentiful cytoplasm with or without granules. They can thus be divided cytologically into small lymphocytes, large lymphocytes and large granular lymphocytes. On ultrastructural examination, their features are very variable: there is heavy chromatin condensation, the cytoplasm may or may not contain acid phosphatase-positive granules, and may contain mitochondria; there are abundant free ribosomes, variable amounts of rough endoplasmic reticulum and usually a small and inactive Golgi apparatus.[2]

Functionally, lymphocytes are divided into B cells, T cells and natural killer (NK) cells. B cells migrate to tissues and differentiate into memory B cells and Ig-secreting plasma cells. T and NK cells are involved in cellular immunity, both innate and adaptive.[5] Their functions are summarized in Table 1. Lymphocytes recirculate between the blood and tissues. Their lifespan is very variable. ◆

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Clinical Review

Clinical Review identifies issues in the medical literature of interest to clinicians in Africa. Essential references are given at the end of each section

Family medicine and primary care

Indications for tonsillectomy

When I moved last year to a new position in a different province of South Africa, I noticed that there seemed to be a high tonsillectomy rate in primary and secondary care. In the previous areas where I have worked, we rarely did such procedures but here I found that there is a weekly tonsillectomy list in the theatres of a number of the small hospitals I visited. I had assumed this to be a local problem. However on a recent trip I was in discussion with a general surgeon from Kenya who talked about the problem of surgical trainees going to rural hospitals and performing procedures that they should not necessarily be doing, with tonsillectomies being included in that list.

Following what I saw, I found an article published last year that looked at the issue of rates of tonsillectomy.[1] The authors found that it is a commonly performed procedure internationally but that there is wide variation in rates (190 - 850/100,000 people ≤19 years of age). They therefore carried out the study to look at the rate in the private health sector in South Africa with regional variations and compare this to international rates. The authors found that the rate was more than double the highest reported national tonsillectomy rate (1,755/100,000 in 2013) and varied regionally within the country. There is no evidence of an increased burden of disease that relates to this. The authors conclude that the variation is due to differences in training and clinical practice, and thus is to some extent a cultural issue amongst medical practitioners. They argue for the development of evidence-based locally relevant indications for tonsillectomy to guide clinical practice.

An article published in the *American Journal of Otolaryngology* earlier this year from Egypt looked at the management of recurrent tonsillitis in children.[2] They compared two antibiotic regimens namely azithromycin and Benzathine penicillin and found these to be equally effective in the reduction of recurrence to each other but also similar to the results obtained with tonsillectomy. A Cochrane review on tonsillectomy versus nonsurgical treatment for chronic or recurrent acute, tonsillitis indicated that there is a small reduction in the number of episodes of sore throat in children in the first year after surgery compared to nonsurgical treatment.[3] The authors note the two studies show there was no significant difference in quality of life outcomes and one study showed no difference in analgesic consumption. In terms of adults there is insufficient evidence on the effectiveness of tonsillectomy. They note that potential benefits of surgery should be weighed against the risks which are not insignificant. In summary it seems that they may be some indications for tonsillectomy in children with chronic and recurrent tonsillitis but tonsillectomy for tonsillitis is difficult to justify in adults.

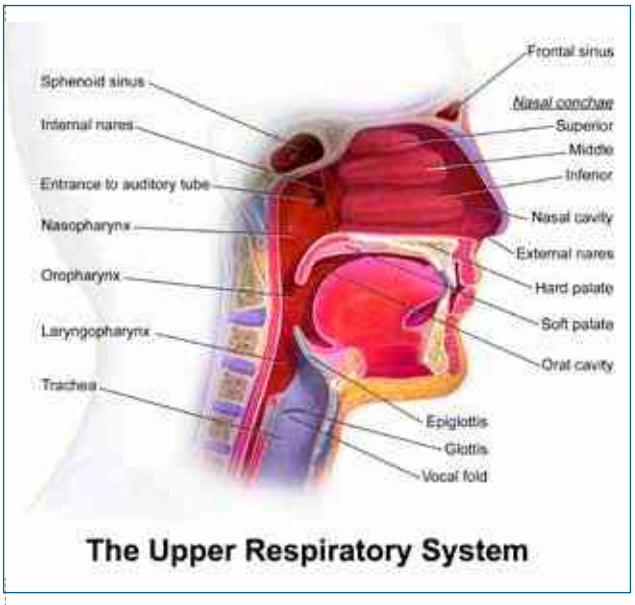
A review paper published last year on indications for tonsillectomy noted that clinical guidelines often include peritonsillar abscess, but suggested that on the basis of evidence, tonsillectomy as first-line treatment is not indicated and should be limited to patients with recurrences, complications or a history of recurrent tonsillitis.[4] Further the author states that tonsillectomy compares to antibiotic therapy and thus because of the considerable post-operative morbidity there needs to be clear indications around the number of episodes required to justify tonsillectomy as opposed to any other treatment. Once again, the need for appropriate, local, evidence-based guidelines is clear.

Upper respiratory tract infections

It is not only the tonsillectomy that is overused in treating tonsillitis but more broadly antibiotics in the treatment of sore throats and other respiratory tract infections. One does not have to look far in both the scientific and the lay press to find articles about the level of abuse of antibiotics and the dangers brought about by this ongoing problem, especially increasing resistance and the rise of superbugs. A recent CPD article in South African Family Practice about the management of colds and flu[5] is worth reading, because I have noted that many colleagues use the two terms interchangeably as if they are the same illness. The authors make the important point that the common cold and flu are two very different viruses with similar symptoms but there is no place for antibiotic usage in either. In fact despite the widespread use of antibiotics for these conditions, justified by physicians on the basis of shortening the length of the illness or preventing superinfection, they note that there is no clinical evidence suggesting that antibiotic use can alter the course of the disease or prevent secondary infection. Treatment of course should be symptomatic.

It is clear that there are many respiratory tract infections are over treated with antibiotics, despite the fact that most are viral in origin.[6] The World Health Organization (WHO) has called for the development of national action plans in regard to overprescribing. Just this month, an article in the Medical Journal of Australia has advocated for a national strategy to reduce overprescribing in general practice.[7] The WHO indicates that antibiotics are prescribed in 45.9% of patient encounters in Africa, as opposed to a reference value of less than 30%.[8]

Given the problem of the overuse of antibiotics in upper respiratory tract infections, one proposed strategy is that of delayed antibiotics: instead of prescribing antibiotics when the patient presents, if the patient is assessed to have a respiratory tract infection they can



The Upper Respiratory System

be given symptomatic treatment and advice, and asked to return if they are not improving or there is any deterioration the condition. In some health systems prescriptions can be given with instructions to the patient that they wait for two days before deciding whether to fill the prescription. An updated Cochrane review published earlier this year looked at the effects on clinical outcomes and other factors of delayed prescription of antibiotics in respiratory tract infections.[9] They found that for many clinical outcomes either strategy produced the same results. While they were some better patient satisfaction with delayed antibiotics there was not as great a reduction in antibiotic use as there is with not using it at all. Basically the conclusion is that when clinicians feel it is safe not to prescribe antibiotics immediately for people with respiratory infections no antibiotics with advice to return if symptoms do not resolve is likely to result in the least use of antibiotics while still maintaining patient satisfaction and clinical outcomes; where clinicians are not confident to do, delayed antibiotic use is a strategy that is acceptable.

Clinicians often respond that patients or their parents demand antibiotics. A study reported in the annals of family medicine looked at the attitudes of parents towards the use of antibiotics in acute respiratory tract infections with children.[10] They noted the fact that parents have misguided beliefs about the role and value of antibiotics and overestimate their benefits. The authors highlight the need for improved communication and shared decision-making around antibiotic use. The above-mentioned Cochrane review on delayed prescribing suggests that patient satisfaction can be maintained with appropriate explanation.

Another Cochrane review published this year addresses the issue of worldwide health threat of antibiotic resistance by looking at effects of interventions aimed at influencing clinician antibiotic prescribing behaviour for acute respiratory tract infections.[11] They found evidence that point of care C-reactive protein testing, shared decision-making and procalcitonin-guided management reduce antibiotic prescribing. (In February, 2017, the US Food and Drug Administration approved the use of procalcitonin, a blood infection marker, to guide antibiotic therapy in patients with acute respiratory infections.)[12] They note however that most research was undertaken in high countries. Given the widespread abuse of antibiotics in Africa, it is critical that we develop locally relevant strategies for addressing the problem. The use of Centor's criteria, an old approach recently re-evaluated, may provide a more practical approach that could be incorporated into our primary care.[13]

Ultimately it is important that we as clinicians need the recent call in Lancet Infectious Diseases that 'all health-care providers who prescribe antibiotics need to take ownership, engage in stewardship, and understand the societal burden of inappropriate antibiotic use.'[14, p.e56.]

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AIDS

The epidemiology of the HIV/AIDS epidemic and the scale up of antiretroviral therapy (ART) in 2016 was described by the joint United Nations Programme on HIV/AIDS (UNAIDS).[1,2] By December 2016, there were an estimated 36.7 (30.8–42.9) million people living with HIV/AIDS (PLHIV) globally, of whom 94% were adults and 6% were children under 15 years of age. In 2016, 1.8 (1.6–2.1) million people were newly infected with HIV and 1.0 (0.83–1.2) million people died from HIV/AIDS. Compared with the previous year, HIV incidence and HIV mortality were slightly lower.

Sub-Saharan Africa (divided now in UNAIDS reports into Eastern / Southern Africa and Western / Central Africa) bears the brunt of this epidemic, as it has done for the last two decades, with 25.5 million adults and children (69% of global total) living with HIV in 2016.[1,2] There were 1.16 million new HIV infections (64% of global total) and 730,000 deaths (73% of global total). Of the 160,000 new HIV infections globally in children, 137,000 (86%) occurred in sub-Saharan Africa. Southern Africa remains the worst affected region on the continent as it accounts for 76% (19.4 million) of the region's disease burden. Within this region, South Africa continues to have the largest HIV/AIDS epidemic in the world with an estimated 7.1 million people living with HIV.

By the end of 2016, there were 19.5 million people globally receiving ART, representing 53% of all people living with HIV.[1,2] In sub-Saharan Africa there has been excellent progress in terms of access to treatment, with over 13.8 million people on ART by 2016. In the world's most affected region, Eastern and Southern Africa, the number on treatment has more than doubled since 2010, reaching 11.7 million, representing 60% of people living with HIV. South Africa alone has almost 3.9 million people on treatment, more than any other country in the world. After South Africa, Kenya has the largest ART programme in sub-Saharan Africa with 1.0 million people on therapy by 2016, with Mozambique (990,000), Zimbabwe (980,000), Uganda (940,000), Tanzania (850,000) and Zambia (800,000) following closely behind.[1,2]

Since 2010, the annual number of new HIV infections (all ages) has declined by about 16%, but the pace of decline is far too slow to reach the Fast-Track Target agreed upon by the United Nations General Assembly in 2016.[1,2] However, sub-Saharan Africa is not doing badly: the steepest decline in new HIV infections between 2010 and 2016 was achieved in Eastern and Southern Africa (29% decline) with Western and Central Africa achieving a 9% decline. In contrast, in some regions of the world, the trend in new HIV infections is either stable (for example, Latin America) or increasing (for example, in Eastern Europe and Central Asia the annual number of new infections has increased by 60%).

This being said, there is no room for complacency in sub-Saharan Africa. Adolescent girls and young women in this region are still at particularly high risk of HIV infection due to poor access to education / sexual and reproductive health services, poverty, food insecurity and violence.

Advances in Antiretroviral Therapy Regimens

The consolidated WHO guidelines launched in July 2016 recommended that ART should be offered to any PLHIV regardless of WHO clinical stage or CD4 cell count and this includes adults, pregnant and breast feeding women, adolescents and children. Since 2016, WHO has been recommending new alternative ARV drug options: dolutegravir (DTG) and efavirenz 400 mg (EFV400) for first-line therapy, and darunavir / ritonavir (DRV/r) and raltegravir (RAL) for second- and third-line therapy.[3]

For first-line treatment, DTG is associated with higher antiretroviral efficacy, better tolerability, lower rates of treatment discontinuation, a higher genetic barrier to resistance and fewer drug interactions compared with other ARV drugs. EFV400 has comparable efficacy and improved safety compared with EFV at the standard dose of 600 mg daily. These two alternative first-line options are now becoming available in low- and middle-income countries (LMIC) as generic fixed-dose combinations at lower prices than the current preferred first-line regimens in use. Although the DTG- and EFV400-containing regimens have clinical and programmatic advantages compared with current standard first-line ART, there is little experience with their use in LMIC. More evidence is needed in these settings and for specific high risk-populations about efficacy and safety, especially during pregnancy.

In second-line therapy, the DRV/r co-formulation is comparable with other boosted protease inhibitors with no significant differences in terms of adverse reactions or treatment discontinuation, hence supporting its use as an alternative medication in second-line regimens. RAL has been approved for children, adults and pregnant women and is effective and well tolerated for second- and third-line regimens after failure of protease-inhibitor-based regimens. Currently, the prices of formulations for these second-line drugs from the pharmaceutical companies, the pill burden and the lack of affordable generic fixed-dose combinations limit their large scale use in LMIC, but this is likely to change in the near future.

The development of new and better ARV drugs is a fast moving field. Two new drugs (cabotegravir and rilpivirine) are in development as long-acting injectable formulations, with a recently published 96-week duration, non-inferiority trial in North America and Europe demonstrating similar efficacy, acceptability and tolerance compared with the current three-drug oral therapy.[4] While it will be challenging for ART programmes in LMIC to keep pace with these new advances and especially to translate them to implementation in the field, it will be important for them to do so, given the increasing prevalence of HIV drug resistance. This has increased from 11% to 29% since the global roll-out of ART in 2001, with some countries (for example,

Uganda, Zimbabwe and Namibia) seeing pre-treatment drug resistance rates (primary resistance) surpassing 10%.[5]

Preventing, diagnosing and managing co-morbidities, including tuberculosis and hypertension

Although it is recommended that PLHIV can start ART as soon as they are diagnosed, more than a third of persons present late with advanced HIV-related disease and up to 10% may die soon after starting therapy.[6] The REALITY trial in Uganda, Zimbabwe, Malawi and Kenya showed that a package of trimethoprim-sulfamethoxazole, isoniazid-pyridoxine, fluconazole, azithromycin and albendazole given to PLHIV starting ART with CD4 cell counts < 100/mm3 was associated with a 27% lower rate of death at 24-weeks compared with standard prophylaxis of just trimethoprim-sulfamethoxazole.[7] The lower death rate was accompanied by reduced risks of tuberculosis, cryptococcal infection and oral / oesophageal candidiasis.

However, there are two caveats with regards to the implications of these findings from the REALITY trial. First, widespread use of fluconazole and azithromycin may potentially increase the risk of antimicrobial resistance to the two drugs. Second, the WHO's recommended "HIV Test and Treat" approach in general obviates the need for baseline CD4 cell counts, as everyone who is HIV-positive is eligible for ART. Nevertheless, CD4 cells counts are crucial for assessing the risk of severe disease and in the context of this trial they were necessary for deciding who would benefit from blanket antimicrobial prophylaxis. HIV/AIDS programmes will need to weight up the advantages and disadvantages of implementing such an approach.

A follow-up of the TEMPRANO ANRS 12136 trial in Cote d'Ivoire assessed the benefits of early ART and 6-months isoniazid preventive therapy (IPT) among PLHIV for a median time of 5 years. 6-months IPT was associated with 37% reduction in mortality regardless of when ART was started and regardless of baseline CD4 cell count or baseline interferon gamma-release assay.[8] The study has important implications. The findings strongly suggest that IPT should be added to ART in any PLHIV provided there is no evidence of active tuberculosis, but whether isoniazid should be for six-months or longer is contextual and relates to the amount of tuberculosis in the community. An editorial accompanying this paper strongly supports the findings, arguing that large numbers of deaths could be avoided if the strategy was accepted and implemented.[9]

Finally, PLHIV have higher frequencies of risk factors for cardiovascular disease that include cigarette smoking, unfavourable lipid profiles and endothelial dysfunction compared with HIV-negative persons. Hypertension is one of the modifiable biological risk factors. In one cross-sectional study amongst PLHIV attending a large University teaching Hospital in Nigeria, 19% had hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or self-reported pharmacological treatment for hypertension) at registration and a further 31% developed hypertension twelve months after starting ART, with increasing age and body mass index being important independent risk factors.[10] While more needs to be done in sub-Saharan Africa to understand the association between ART and hypertension, it makes sense for ART programmes to start thinking now about integrating services for non-communicable diseases. Measurement of blood pressure is a relatively easy activity to start with, and ART programmes need to work out how to do this and also how to manage hypertension once it is diagnosed.

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Infection

Third vaccine for mumps outbreaks

Receipt of a third dose of the measles-mumps-rubella (MMR) vaccine has been shown to help combat mumps outbreaks. The study was conducted during an outbreak of mumps in students at the University of Iowa. Of the 2015-2016 academic year enrolment cohort (over 20,000 students), 259 were diagnosed with mumps. Before the outbreak, 98% of students had been given at least two doses of the MMR vaccine. A third dose was given to nearly 5000 students during the outbreak. Those given a third dose had a lower risk of mumps than those who had only received two doses (6.7 versus 14.5 cases per 1,000). The vaccine was also shown to wane over time as an increased risk of mumps was found in students who had received their second and final dose 13 years or more before the outbreak. A third dose of MMR vaccine may improve mumps outbreak control.

Cardemil CV, Dahl RM, James L, et al. Effectiveness of a third dose of MMR vaccine for mumps outbreak control. NEJM 2017; 377:947-956.

Long-acting antiretroviral injections

Two antiretroviral drugs are being investigated for efficacy as long-acting maintenance therapies for HIV-1 viral suppression. The two drugs, long-acting cabotegravir and rilpivirine, have been investigated for efficacy when combined in a randomised phase 2b, open label study. Treatment naïve HIV-1 positive adults were started on oral therapies (oral cabotegravir plus abacavir–lamivudine) once daily for a 20-week induction period and were then assigned to a regimen of either 4-weekly or 8-weekly cabotegravir plus rilpivirine intramuscular injections or continued daily oral therapies. Nearly 300 participants took part in the maintenance portion of the study following the induction period. Viral suppression at week 96 was maintained in 84% of participants receiving oral treatment, 87% in the 4-weekly group and 94% in the 8-weekly group. Two-drug injections of the long-acting antiretrovirals cabotegravir and rilpivirine given at either 4 or 8 week intervals were well tolerated and as efficacious in maintaining suppression of HIV viral load as daily oral therapy up to 96 weeks.

Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. Lancet 2017; 390:1499-1510.

Candidate mRNA based vaccine for rabies

Preclinical models suggest that mRNA based vaccines are safe and immunogenic. A phase 1 study based in Germany has just reported its findings of a first-in-human proof-of-concept trial for a prophylactic mRNA-based vaccine encoding rabies glycoprotein (CV7201). Eligible volunteers were healthy adults, aged 18-40 years, with no prior rabies vaccination. Participants (n=101) received three doses of CV7201 either intradermally or intramuscularly by a needle-syringe or one of three needle-free devices. The primary endpoint was safety and tolerability of the vaccine and a further outcome was to establish the lowest dose of CV7201 that could neutralise the rabies virus (closest to the WHO-specified titre). When administered by needle-free device the immune response was favourable and met WHO-specified titres, however, it was shown to be ineffective with needle-syringe injection. Injection site reactions were reported in 94 and 97 per cent of intradermally and intramuscularly vaccinated participants and 10 grade 3 systemic adverse events were reported. Needle-free administration of this mRNA-based vaccine may be effective and against rabies and generally tolerable. The study continues for long-term safety and immunogenicity follow up.

Alberer M, Gnad-Vogt U, Hong HS, et al. and immunogenicity of a mRNA rabies vaccine in healthy adults: an open-label, non-randomised, prospective, first-in-human phase 1 clinical trial. Lancet 2017; 390:1511-1520

Review of cholera vaccine efficacy

Cholera outbreaks hit resource-poor settings and can devastate the populations they touch. Killed whole-cell oral cholera vaccines (kOCVs) are emerging as standard management. However, studies on efficacy of kOCVs have produced varied results, presenting a challenge for public health policy makers. To better understand the effectiveness of kOCVs a group has conducted a meta-analysis and systemic review, aiming to linearise results and calculate average estimates of kOCV efficacy. Data were extrapolated from seven randomised trials and six observational studies, totalling information from 700 patients. Two-dose efficacy estimates showed that vaccine efficacy in children was better in those five years old and over, compared to those under five. For all patients, two-dose efficacy estimates averaged 56% in the first year and 59% in the second year. However, the average efficacy decreased to 39% in year four. The cholera protective effect of two kOCV doses may last for up to 3 years, but wane after that. One dose may be protective at least in the short term, which could have important implications for management in an outbreak setting.

Bi Q, Ferreras E, Pezzoli L, et al. Protection against cholera from killed whole-cell oral cholera vaccines: a systematic review and meta-analysis. Lancet Infectious Diseases 2017; 17:1080-1088

Respiratory

Management for mild COPD

Chronic obstructive pulmonary disease (COPD) patients can suffer from a decreased lung function over time. Despite this, few mild sufferers receive medication due to presenting with few symptoms. A trial conducted in China has investigated if the use of tiotropium, a long-acting anticholinergic bronchodilator given to improve airflow and COPD symptoms, may benefit those with mild COPD and ameliorate the decline in forced expiratory volume in 1 second (FEV1) results that occurs with decreased lung function over time. Participants were of COPD Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1 (mild) or stage 2 (moderate) severity. Participants were randomised to receive either tiotropium (n=388) or placebo (n=383) once daily for two years. At 24 months, the patients who had received tiotropium had a significantly higher FEV1 than those given placebo. The annual decline in FEV1 was significantly less versus placebo in the tiotropium group after bronchodilator use but not before bronchodilator use. Early-stage COPD of GOLD stage 1 or 2 patients may benefit from the use of daily tiotropium to help prevent declining FEV1.

Zhou Y, Zhong N, Li X, et al. Tiotropium in early-stage chronic obstructive pulmonary disease. NEJM 2017; 377;923-935.

Add-on therapy for uncontrolled asthma

It is estimated that over 50 million people suffer from mild-to-severe uncontrolled asthma, globally. These patients often experience quality-of-life reducing exacerbations that require medical help, despite being on maintenance therapies. One study has set out to investigate if asthma

might better be controlled with the use of add-on macrolide antibiotic therapy to patients on concurrent maintenance treatment of inhaled corticosteroid and long-acting bronchodilator. Participants on the above maintenance therapy were randomly assigned to receive either additional oral azithromycin (n=213) or placebo (n=207) three times a week up to 48 weeks. By the end of the trial the treatment group given Azithromycin experienced a significantly lower rate of asthma exacerbations and an improved asthma-related quality of life compared to the placebo group. It was also found that diarrhoea was significantly more common in azithromycin receiving patients versus placebo. Oral azithromycin given to mild-to-severe uncontrolled asthmatics as an add-on therapy to maintenance treatment can help improve symptoms.

Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. Lancet 2017; 390: 659-668

Biomarker for COPD progression

Respiratory airway mucins are implicated in the poor transport of mucus seen in sufferers of COPD. The use of respiratory airway mucin concentration as a biomarker of COPD has been investigated. It was theorised that high mucin concentrations may be implicated in the disease progression of chronic bronchitis, a feature of COPD sufferers. The study looked at total mucin concentrations in over 900 COPD sufferers. Mucin concentrations were highest in severe COPD participants who were current or former smokers versus controls with no history of smoking and were higher again in participants with a history of two or more COPD exacerbations per year. The researchers concluded that airway mucin concentration could be a potential candidate for a diagnostic biomarker and therapeutic target of chronic bronchitis in COPD sufferers.

Kesimer M, Ford AA, Ceppe A, et al. Airway mucin concentration as a marker of chronic bronchitis. NEJM 2017; 377:911-922.

Chronic cough in idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a progressive condition that critically reduces length of life. Eighty percent of those with IPF suffer from a debilitating cough that is not often responsive to medical therapies. A phase 2 trial has investigated the safety and efficacy of nebuliser-administered PA101, a formulation of sodium cromoglicate. Two patient groups were included, IPF patients with chronic cough (n=24) and patients with chronic idiopathic cough (CIC) (n=27). The randomised, double-blind, placebo-controlled trial ran in centres across the UK and the Netherlands. Participants were given 3 doses of drug or placebo via oral inhalation for 2 weeks, followed by a 2 week wash out period and then 2 weeks of treatment in the opposite arm of the study. In patients with IPF, PA101 was effective in reducing frequency of daytime coughing by 31% compared to placebo. However, PA101 was not effective in CIC. The therapy was well tolerated among both patient groups. The researchers suggested that PA101 may work against coughs in an IPF-disease specific manner, warranting further investigation.

Birring SS, Wijsenbeek MS, Agrawal S, et al. A novel formulation of inhaled sodium cromoglicate (PA101) in idiopathic pulmonary fibrosis and chronic cough: a randomised, double-blind, proof-of-concept, phase 2 trial. Lancet Resp Med 2017; 5:806-815

Obs & Gynae

Post-caesarean infection in obese women

As the incidence of obesity rises it is becoming increasingly important for medical practice to adapt in order to minimise the risks associated with obesity. Obese women are known to have an increased risk of post-caesarean surgical site infection (SSI). A group of researchers in Ohio, USA have investigated whether the use of prophylactic postpartum antibiotics, given with usual preoperative cephalosporin prophylaxis helps combat SSI incidence in obese women following caesarean delivery. In this double-blind trial 403 participants were randomly assigned to receive standard preoperative antibiotic prophylaxis of cephalosporin and either oral cephalexin and metronidazole (n=202) or placebo (n=201) every 8 hours for 48 hours following caesarean delivery. At 30 days' post caesarean, the rate of SSI in the postpartum antibiotic group was 6% compared to 15% in the women given placebo. No serious adverse events were reported in either group. Standard preoperative antibiotic prophylaxis may be more effective when combined with 48-hours of postoperative oral cephalexin and metronidazole for protection against surgical site infection in obese women undergoing caesarean.

Valent AM, DeArmond C, Houston JM, et al. Effect of post–caesarean delivery oral cephalexin and metronidazole on surgical site infection among obese women: A randomized clinical trial. JAMA 2017;318(11):1026–1034. doi:10.1001/jama.2017.10567

Breastfeeding and endometriosis

Endometriosis is a chronic disorder that can place a huge burden on the wellbeing of those affected. It is theorised that breastfeeding may be protective against endometriosis due to the low oestrogen environment. Otherwise, oestrogen presence can stimulate maintenance and growth of endometriosis lesions. A prospective cohort study set out to investigate this possible link in a study involving over 7,000 women with a history of one or more pregnancies. Breast feeding duration total, exclusive breast feeding, and postpartum amenorrhea were reported. The main outcome of the study was laparoscopically confirmed endometriosis. Women who reported a total lifetime duration of breastfeeding at less than one month were found to have an incidence of endometriosis at 453 cases per 100,000 person years versus 184 cases per 100,000 when breastfeeding for a lifetime total of ≥ 36 months. Duration of total and exclusive breastfeeding were significantly associated with a decreased risk of endometriosis. It is likely this link is due to postpartum amenorrhea and other factors. This highlights a potentially beneficial modifiable behaviour for pregnant women that could moderate risk for endometriosis.

Farland LV, Eliassen AH, Tamimi RM, et al. History of breast feeding and risk of incident endometriosis: prospective cohort study. BMJ 2017; 358 :j3778

Interventions for gestational weight gain

Obesity and excessive weight gain in pregnancy can have negative outcomes for mother and child, both during pregnancy and in later life. This is emerging as a real problem, especially when considering that estimates predict half of all women of childbearing age are overweight or obese. A systematic review and meta-analysis has been conducted to assess effects of dietary and physical interventions on pregnancy outcomes, in particular, gestational weight gain and maternal and offspring outcomes. Data from over 12,500 women from 36 randomised trials was included in the analysis. Intervention groups did result in a lower gestational weight gain than control groups. The study could not find a significant reduction in odds of adverse neonatal and maternal outcomes with diet and physical based

interventions. Data from 32 of the studies showed strong evidence supporting the effect of interventions in reducing the odds of pregnant woman needing a caesarean section for delivery. Dietary and physical interventions during pregnancy can help reduce weight gain in pregnancy.

International Weight Management in Pregnancy (i-WIP) Collaborative Group. Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials. BMJ 2017; 358 :j3119

Postpartum depression

One of the most common postnatal complications is postpartum depression (PPD), affecting 5-15% of all women following childbirth. There are long term impacts of PPD that can influence both the mother's risk of long term depression and the child's development. A research group has carried out a study to estimate the incidence of postpartum affective disorder (AD), duration of treatment, and rate of subsequent postpartum AD in women with no prior psychiatric history. The study was conducted using a cohort of women taken from Danish national registers and included over 457,000 women who prior to their firstborn child had no psychiatric medication or hospital contact history. Postpartum AD occurred with 0.6% of births. For those women affected, 28% of women were still on treatment one year after treatment initiation and 5% at 4 years. Women with PPD and psychiatric hospital contact following their first birth had a 46 times higher rate of a recurrent episode following a second birth, and those who were given antidepressants for PPD had a 26 times higher rate than women with no postpartum AD history. Rasmussen M-LH, Strøm M, Wohlfahrt J, et al. (2017) Risk, treatment duration, and recurrence risk of postpartum affective disorder in women with no prior psychiatric history: A population-based cohort study. PLoS Med 14(9): e1002392. https://doi.org/10.1371/journal.pmed.1002392

Pregnancy outcomes with dengue

Dengue is a mosquito transmitted disease with a high morbidity, mortality and economic burden. Over recent years it has had a huge impact on Brazil with over 5,000 deaths since 2002. There are increasing rates of infection among infant, elderly and pregnant groups. However, few studies have monitored the impact of dengue in pregnancy on foetal outcomes. With this is mind, a group has looked at birth outcomes among pregnant women in Brazil who had a symptomatic dengue infection during pregnancy between 2007 and 2013 via a retrospective observational cohort study. Data were taken from 3,898 dengue-positive women, 3,100 dengue-negative women, and 3,800 newborn babies (taken from a reference population). Birthweight did not seem to differ between groups. Across all groups, the prevalence of congenital malformations was lower than one percent. After adjusting for cofounders, analysis showed that risk of preterm birth was higher in women who were positive for dengue versus the non-dengue group.

Nascimento LB, Siqueira CM, Coelho GE, et al. Symptomatic dengue infection during pregnancy and livebirth outcomes in Brazil, 2007–13: a retrospective observational cohort study. Lancet Infectious Diseases 2017. 17:949-956.

Paediatrics

Biomarker for antibiotic therapy guidance

In high income countries, the prevalence of early-onset sepsis in late-preterm and term neonates is confirmed, at most, in 0.1% of infants. Despite this, up to 7% of infants are given antibiotics for suspected early-onset sepsis in the first three days of life. Procalcitonin is one of the most competent biomarkers of severe bacterial infections in neonates. A randomised trial conducted across Dutch, Swiss, Canadian and Czech hospitals has investigated if the use of a procalcitonin-guided decision making strategy could help reduce the frequency and duration at which such neonates are given antibiotics. Over 1,700 eligible neonates were enrolled in the study and randomised to receive either procalcitonin-guided therapy (n=866) or standard therapy (n=844). Duration of antibiotic therapy was significantly reduced in the group whose care was guided by procalcitonin. Further outcomes of non-inferiority for re-infection or death could not be assessed due to the low occurrence and absence of these, respectively. For infants with suspected early-onset sepsis a procalcitonin-guided decision making approach was superior to the standard care in reducing potentially unnecessary antibiotic therapy.

Stocker M, van Herk W, el Helou Salhab, et al. Procalcitonin-guided decision making for duration of antibiotic therapy in neonates with suspected early-onset sepsis: a multicentre, randomised controlled trial (NeoPIns). Lancet 2017; 390:871-881

Childhood inflammatory bowel disease and cancer

It is well-documented that inflammatory bowel disease (IBD) is a risk factor for the development of cancers, particularly gastrointestinal. However, much of the research that has informed us on this area has been conducted using patients with adult-onset IBD. There is an increasing prevalence of paediatric Crohn's, this combined with the fact that there have been changes to bowel disease management over the years, warrants further investigation into the prevalence and impact of childhood-onset IBD. Data were taken from a Swedish national patient register and 9405 cases of childhood onset IBD (<18 years) were included and matched to over 92,000 comparators. After an average follow-up of 27 years, 3.3 per 1,000 person years with childhood-onset IBD developed primary cancers, compared to 1.5 per 1000 person years in the matched controls. Those with childhood-onset ulcerative colitis and Crohn's disease had hazard ratios of 2.6 and 1.7, respectively, for any cancer. The relative risk for gastrointestinal cancers for those with IBD was 18. The risk of cancer following childhood-onset IBD has not declined over time.

Olén O, Askling J, Sachs MC, Frumento P, NeoviusM, Smedby KE et al. Childhood onset inflammatory bowel disease and risk of cancer: a Swedish nationwide cohort study 1964-2014. BMJ 2017; 358 :j3951

Acute kidney injury

Combination antibiotic therapy is a common management strategy for hospitalised children when battling serious infection. For adults, combination therapy of intravenous (IV) vancomycin plus piperacillin sodium/tazobactam sodium is associated with a higher risk of acute kidney injury (AKI) versus combination therapy of vancomycin plus one other ß-lactam antibiotic. Researchers now want to establish if this combination is safe in children by investigating the risk of AKI. The retrospective cohort study included children aged between 6 months and 18 years (n=1915) given IV vancomycin plus one other antipseudomonal ß-lactam combination therapy during a hospitalisation period of 3 or more days. The particular combination of IV vancomycin plus piperacillin/tazobactam was associated with higher odds of children developing AKI versus vancomycin plus one other antipseudomonal ß-lactam combination. Vancomycin combination therapy with piperacillin/tazobactam, given intravenously, may increase risk of acute kidney injury in hospitalised children. The researchers recommend that paediatricians be cautious

when considering combination therapies in hospitalised children.

Downes KJ, Cowden C, Laskin BL, et al. Association of acute kidney injury with concomitant vancomycin and piperacillin/tazobactam treatment among hospitalized children. JAMA Pediatr. 2017. doi:10.1001/jamapediatrics.2017.3219

Increasing fat-free tissue in malnourished children

Children from low-income countries have high rates of moderate acute malnutrition (MAM) which can lead to morbidity and death. It is imperative that optimum management strategies are investigated to help improve the health of the millions of children with MAM to prevent the adverse downstream outcomes. And indeed, further research on food supplements has been recommended by the World Health Organisation. Currently, lipid-nutrient supplement (LNS) and corn-soy blends (CSB) are both of intrigue but there is some concern that LNS may cause accumulation of fat tissue. Previous studies have focused on total weight gain, not composition of weight gain, which can impact a child's health if too fatty. A large trial included over 1,500 children with MAM in Burkina Faso, West Africa. The study investigated effectiveness of supplemental foods, using measurements of body composition to assess weight gain and fat-free tissue. The study found that fat-free tissue was best increased using LNS based supplement compared to CSB supplements. The researchers support wider use of LNS to help manage children with moderate acute malnutrition.

Fabiansen C, Yaméogo CW, Iuel-Brockdorf A-S, et al. Effectiveness of food supplements in increasing fat-free tissue accretion in children with moderate acute malnutrition: A randomised 2 × 2 × 3 factorial trial in Burkina Faso. PLoS Med 2017; 14(9): e1002387.

Miscellaneous

Durability of bariatric surgery benefits

Positive short term outcomes for those who have received bariatric surgery are well documented, including improved metabolic profiles for conditions such as type 2 diabetes. A study has set out to assess the long-term impact of bariatric surgery on patient's health at 12 years' post-surgery. Over 1,000 patients with severe obesity were included in the study, 418 of which had undergone Roux-en-Y gastric bypass surgery. The remainder of patients were split into two groups, those who sought but did not receive surgery, and those who did not seek or receive surgery. The mean weight change at 12 years follow up was -35 kg for the surgical group and -2.9 and 0 kg weight change for the two non-surgical groups. At two years, 75% of the surgery patients who had type 2 diabetes at baseline had remitted (66 of 88 patients), with 51% still in remission at 12 years. For both hypertension and dyslipidaemias, the surgery group had a significantly lower incidence than the non-surgery patients. Weight loss and improved metabolic profiles may be durable following Roux-en-Y gastric bypass surgery.

Adams TD, Davidson LE, Litwin SE, et al. Weight and metabolic outcomes 12 years after gastric bypass. NEJM 2017; 377:1143-1155.

Conservative breast radiotherapy

Patients who have undergone radiotherapy for early-stage breast cancer may have a reduced risk of recurrence by up to 50%. The standard for practice in the United Kingdom is to use whole breast radiotherapy. However, there is a group of thought that more conservative radiotherapy may still be able to produce the same outcomes regarding local recurrence but with fewer adverse effects. A multicentre trial was conducted across 30 radiotherapy sites in the UK involving women who had breast conserving surgery for unifocal early breast cancer. Three groups included participants who were given whole breast radiotherapy (control n=674), reduced-dose whole-breast radiotherapy (n=673), and partial-breast radiotherapy (n=669) for 15 daily treatment fractions. Primary endpoint was ipsilateral local relapse. At 5 years follow up both the reduced-dose and partial-breast radiotherapy were considered non-inferior to standard whole breast radiotherapy with regards to the primary endpoint. Adverse tissue events were similar or lower in the partial and reduced settings. Conservative radiotherapy to the breast for patients with excised, early stage breast cancer may be considered as a reasonable treatment option.

Coles CE, Griffin CL, Kirby AM, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. Lancet 2017; 390:1048-1060

Dental procedures and infective endocarditis

Some evidence suggests a link between invasive dental procedures and the development of infective endocarditis, due to oral streptococci, specifically, in those with prosthetic heart valves. This link is being investigated further following questions raised regarding the use of antibiotic prophylaxis prior to invasive dental procedures. A cohort of over 138,800 adults with prosthetic heart valves living in France were included in the study. Over 100,000 invasive dental procedures were performed between them, 50% of which received antibiotic prophylaxis. After an average follow up of 1.7 years, 267 individuals developed an infective endocarditis that was associated with oral streptococci. There was no significant increased rate of such endocarditis following periods exposed to an invasive dental procedure, and after a procedure given without prophylactic antibiotics, compared to non-exposure. However, following a crossover analysis, it was found that invasive dental procedure exposure was more frequent in a period of 3 months immediately preceding oral streptococcal infective endocarditis, than in the matched control period. The development of infective endocarditis may be influenced by invasive dental procedures in adults with prosthetic heart valves.

Tubiana S, Blotière PO, Hoen B, et al. Dental procedures, antibiotic prophylaxis, and endocarditis among people with prosthetic heart valves: nationwide population based cohort and a case crossover study BMJ 2017; 358 :j3776

CPD Challenge

Questions

Test your knowledge against the Clinical Review articles from pages 31 to 34.

Clinical Review: Family Medicine

1. Which one of the following statements is the most likely explanation for the variation in tonsillectomy rates internationally?
   a. Variations in incidence of streptococcal infections.
   b. Differences in training and clinical practice
   c. Access to surgeons and surgical infrastructure
   d. Global and regional patterns in the burden of diseases.
   e. Social determinants of health
2. Indicate if each of the following statements is TRUE or FALSE
   a. In the management of recurrent tonsillitis in children, tonsillectomy is superior to antibiotic regimens
   b. Tonsillectomy for more difficult to justify in adults than in children
   c. Tonsillectomy should be first-line treatment for peri-tonsillar abscess.
   d. The common cold and flu are caused by two similar viruses.
   e. There is no clinical evidence that antibiotics used in colds and flu can alter the course of the disease or prevent secondary infection.
   f. Delayed antibiotic prescription leads to poorer outcomes than immediate prescription.
   g. Shared decision-making can assist in reducing antibiotic overuse.

Clinical Review: AIDS

The following statements are true for the year 2016:

3. There were an estimated 50 million people globally living with HIV
4. 1.8 million people globally were newly infected with HIV
5. About 70% of all people living with HIV lived in sub-Saharan Africa
6. There were 25 million people on antiretroviral therapy
7. South Africa has the largest HIV epidemic in the world

The following statements are true for HIV-infected persons on ART:

8. ART should be offered to all persons infected with HIV regardless of WHO clinical stage or CD4 cell count
9. Dolutegravir (DTG) is associated with higher antiretroviral efficacy, better tolerability, lower rates of treatment discontinuation, a higher genetic barrier to resistance and fewer drug interactions compared with other ARV drugs
10. Efavirenz 400 mg daily is less effective than efavirenz 600 mg daily
11. The addition of isoniazid preventive therapy to ART has been shown to reduce mortality
12. Hypertension is an important problem to identify and treat in HIV-infected persons on ART.

CPD Answers

Family Medicine

1. b
2. T/F
   a. FALSE
   b. TRUE
   c. FALSE
   d. FALSE
   e. TRUE
   f. FALSE
   g. TRUE

AIDS

3. No
4. Yes
5. Yes
6. No
7. Yes
8. Yes
9. Yes
10. No
11. Yes
12. Yes

One

Two

Three

Four

Five

Quiz answer (See page 40)

Q1 (a), (b), (c). All the answers are relevant, but the priority is to get him quickly into good fluid balance

Q2 (a), (b), (c). The past history is very relevant. It cannot be assumed that this is a simple case of gastroenteritis.

Q3 (a), (b), (c). All three of these answers must be considered. Problems with adhesions may arise many years after intra-abdominal surgery. As for (e) the opposite is the case. A high CRP with a relatively low white cell count suggests viral rather than bacterial infection.

Q4 (b), (c), (d). Choosing (a) could be disastrous as the renal function is compromised: furosemide is contraindicated, as is any diuretic. He had been over-perfused and with the very low serum albumin level his blood vessels were leaking fluid into the tissues. The poor renal function with low urine output compounded the problem.

Q5 (a), (b). There is no evidence for food poisoning (usually bacterial) as the cause. Nor is an allergic reaction feasible.

Hiccups and distended loops (answers on page 39)

Part one

Thomas, a 70-year old man of European descent living in Kenya, was driven by a friend to see his doctor after three days of diarrhoea and vomiting. He had some medical knowledge, so that he had tried to resolve things by drinking copious amounts of watery fluids. By the third day he was very ill.

By this time he was very dehydrated, had a resting pulse rate of 160/minute and his blood pressure was 80/40 mm Hg. His temperature was 37° Celsius, his abdomen was distended, and he had hiccups. With each hiccup spasm he brought up a small amount of dark green bile. He was admitted directly to hospital.

Q1 What are your top three priorities for Thomas?

- **(a) Pass a nasogastric tube and siphon off the stomach contents**
- **(b) Start an intravenous infusion of normal saline**
- **(c) Organise an abdominal ultrasound examination**
- **(d) Insert a urethral catheter into the bladder to estimate fluid balance**
- **(e) Take blood samples (f) Chest Xray (g) Electrocardiogram**

Part two

The nasogastric tube drains copious dark green material, and the abdominal ultrasound reveals distended loops of small bowel. He has no bowel sounds and continues to be distended. His blood pressure is rising to within normal levels, but he still has a tachycardia of around 120/minute. His hiccups continue, exhausting him. Nine years before he had a proximal hemicolectomy for stage 1 cancer of the caecum, and three years before he had a transurethral resection of the prostate for chronic granulomatous prostatitis.

Q2 What are your preliminary thoughts about his current diagnosis?

- **(a) He has a severe viral gastroenteritis causing paralytic ileus.**
- **(b) His small bowel obstruction may be related to adhesions following his bowel surgery.**
- **(c) There may be a problem, such as a stricture, at his ileo-colic anastomosis that would complicate his gastroenteritis.**
- **(d) The past surgery is irrelevant: he has not had symptoms in the 9 years since his bowel surgery.**
- **(e) Severe viral gastroenteritis can present and worsen in this way regardless of the past history.**

Part three

Three efforts to pass a catheter into the bladder failed, so that he had to have a guided endoscopic catheter insertion past a stricture at the base of his bladder. He was left with the catheter in situ. Over the next few days he became severely oedematous, and his urine output declined. At this point his haemoglobin was now 9.1, serum albumin 19, C-reactive protein (CRP) of 200, and estimated glomerular filtration rate (eGFR) 29. His white cell count is only very slightly raised.

Q3 What are your thoughts on these developments?

- **(a) He has been over-hydrated by the intravenous infusion.**
- **(b) He has an acute toxic renal failure linked to the bowel inflammation.**
- **(c) The haemoglobin and serum albumin levels are explained by his haemodilution.**
- **(d) He needs total parenteral nutrition intravenously, having had no nutrition for 8 days: he is starving to death if this continues.**
- **(e) The relatively low white cell count with such a high CRP suggests bacterial food poisoning rather than severe viral infection.**

Part four

Q4 What would you do about the oedema? His BP has risen from his usual 140/75 to 180/110

- **(a) Give a powerful diuretic such as furosemide**
- **(b) Treat him conservatively: as the bowel inflammation recedes and the obstruction eases you can expect the kidneys to recover and a diuresis to start.**
- **(c) Add a BP-lowering agent such as amlodipine that is least likely to harm the kidneys.**
- **(d) Stop the intravenous infusion.**

Part five

After ten days the bowel obstruction eased and the urine flow improved. Colonoscopy showed no problem with the ileocolic anastomosis and a repeat abdominal ultrasound showed a normally functioning bowel. His BP returned to 145/85 mm Hg, his haemoglobin to 13, the CRP dropped to 15, and the eGFR rose to 39. Two months later Thomas was back to his usual life.

Q5 What is your final diagnosis?

- **(a) Acute viral gastroenteritis complicated by post-operative adhesions and toxic renal inflammation.**
- **(b) The renal failure may have been heightened by the urethral stricture causing chronic back pressure on the kidneys.**
- **(c) Food poisoning leading to this series of complications.**
- **(d) An acute allergic reaction in the gut to some ingredient in a meal over the previous 48 hours.**

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