

April 2018 Volume 40 Number 3

# Africa HEALTH

**Malaria: rocking or rolling back?**

**Epilepsy: Misunderstanding seizures**

**Nosocomial infection and infection control**

**Harnessing technocrat skills as proactive leaders**





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Africa Health is a journal of continuing medical education information for physicians and other health professionals in Africa.

Africa Health is published by:  
FSG Africa Ltd  
Vine House, Fair Green, Reach  
Cambridge, CB25 0JD, UK  
Telephone: +44 1638 743633  
Fax: +44 1638 743998  
Email: [editor@fsg.co.uk](mailto:editor@fsg.co.uk)  
[www.africa-health.com](http://www.africa-health.com)

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ISSN 0141-9536 (print)  
ISSN 2053-4760 (online)

Published six times a year by:  
FSG Africa Ltd

Printed in Lagos, Nigeria and  
Nairobi, Kenya

All contents are ©2018  
FSG Africa Ltd.

Front cover: Scanning Electron  
Microscope image of common  
types of bacteria.  
Photo courtesy: Science Photo Library.



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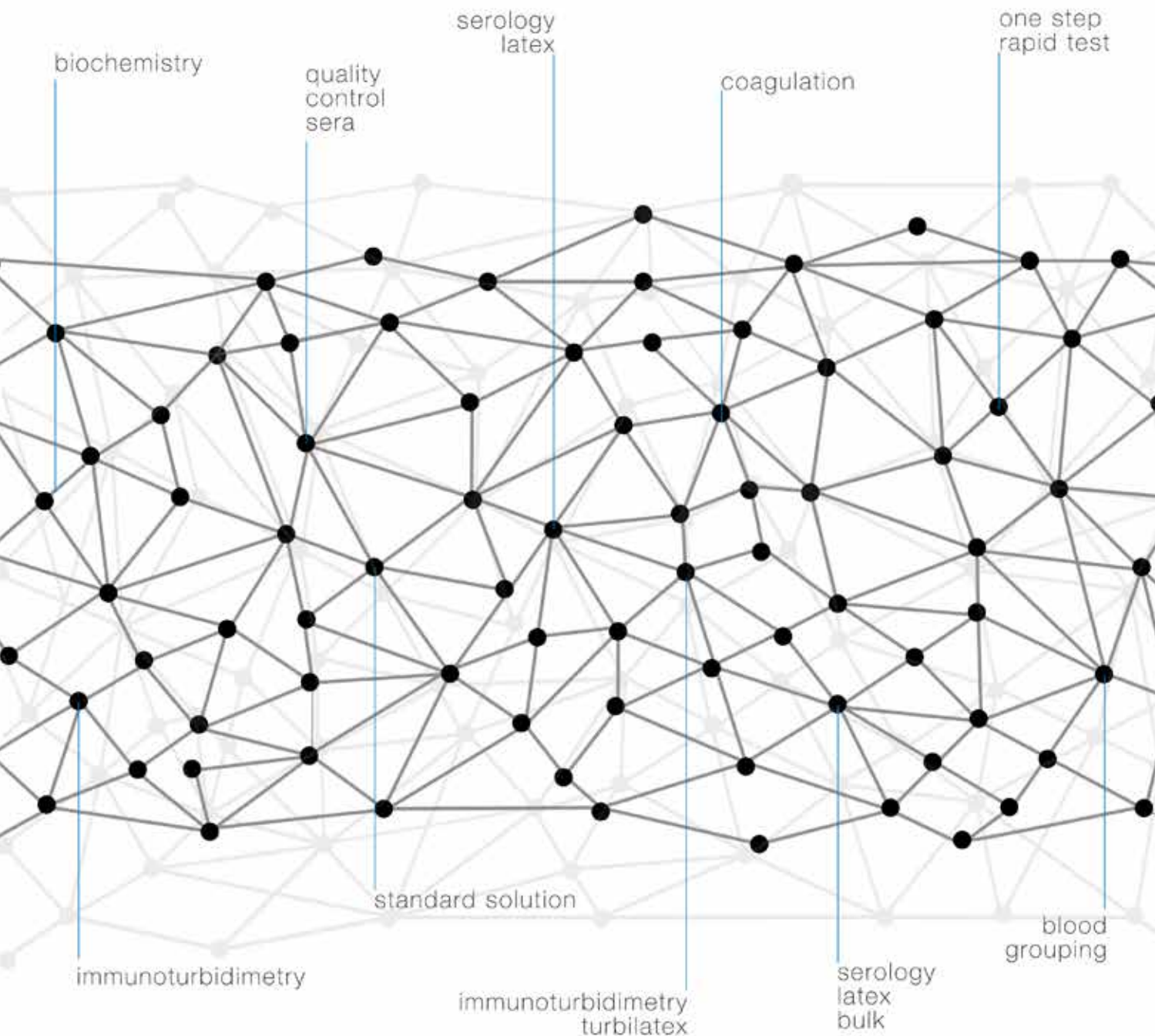
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## Alma Ata rebrands itself to reflect the great Almaty!

This journal was born in the same month as the historic primary healthcare conference was held in Alma Ata, Kazakhstan back in October 1978. This October, the 40th Anniversary of this meeting is being commemorated in the same place, though slightly confusingly for those wishing to link the two, the city has changed its name to Almaty. So Almaty2 is becoming the chosen name of the new Declaration. Through the influential HIFA platform ([www.hifa.org](http://www.hifa.org)), we've been busy inputting to the draft of the Declaration that global health leaders are expected to adopt at the meeting this year. We believe there should be greater emphasis on the availability of quality health information (for both health professionals and consumers). It will be interesting to see if the final draft reflects any of our thoughts, though you may be surprised to hear we are not holding our breath!

Back in 1978 the slogan was 'Health for All by the year 2000'. It was the mantra for hundreds of meetings until sometime in the early 1990s when global health indicators were remaining resolutely static (or negative) and it was quietly buried in the graveyard of international promises. In came the MDGs... and now the SDGs, onto which the slogan/concept Universal Health Care has been tagged.

In a change to our usual format, (and part of our switch to quarterly publication) we take a special look at UHC and its practical relevance on the next four pages. I am a sceptic, believing it puts too much emphasis on health insurance as the financing mechanism rather than political will of governments. With so many Africans working in the informal sector, I cannot see how 'no person shall be left behind', but my co-author, Tarry Asoka, who is much more experienced

at health implementation, can see hope from current strategies. I invite readers to let us have their thoughts on their perspectives of the practicalities of UHC implementation.

On a separate tack, one subject that has been out of the headlines in recent times is breastfeeding. Good to see WHO and UNICEF (see news story) speaking out again on its importance and the need to proactively encourage nursing mothers to put baby to breast. But it reminded me of the time in the early 1990s when we were set with an interesting dilemma. We'd always had a rule that we didn't accept advertising from alcohol, tobacco, or breast milk substitute manufacturers. But in the early era of mother-to-child transmission of HIV through breastfeeding, we were receiving renewed approaches from the milk manufacturers. We could see the argument but decided to consult contacts in WHO and UNICEF to see what their thoughts were. Our contact at WHO responded to say that on balance so long as any ads conformed to the advertising code, OK. Our contact at UNICEF responded indignantly saying if we ever took such an ad, they would never speak to us again! So there we had it. North Pole and South Pole from the two 'authorities'! We've long thought this was a good management school question. What do do? Suffice to say we chose to keep talking with UNICEF.



**Bryan Pearson**  
([bryan@fsg.co.uk](mailto: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.



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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>)





SPECIAL FOCUS

## Universal Health Coverage

### A cautious optimism for UHC in Africa

Despite the cacophony of voices declaring support for Universal Health Coverage (UHC), the World Health Organisation (WHO) says that come 2030 or there about, the organisation would like to see a situation where everyone in the world is able to get the health services they need, without suffering financial hardship when paying for these services. No doubt, encouraging every nation on the globe to reach its people with all health services is a lofty ideal. However, a key question is: haven't we been here before?

Evoke the World Health Assembly 1977 resolution of 'Health for all by the Year 2000'. As this mantra was chanted: 'The main social target of governments and of WHO was the attainment by all the world's people of a level of health that would permit them to lead a socially and economically productive life by the year 2000'. It was envisaged that this global health goal would be implemented by ensuring access to essential primary health care (PHC) and reduction by finite amounts of the burden of disease, disability and premature death. On D-day, out of the welter of words and the plethora of plans, little of practical value emerged and nothing sufficiently potent to end the old and unpleasant ways of doing things happened. Due to several obstacles, in particular the lack of political will to implement measures to achieve this global objective, the Health for all (HFA) agenda was never achieved. The PHC strategy itself was subjected to palliative measures and compromises made for the sake of taking action – but the basic problems



remain. What has changed now? And what are the indications that things might be different this time around?

We are told the main differentiating feature is the inclusion of 'improving financial access'. But this shift in focus is taking a life of its own and now beginning to appear as the real deal. Then and now, policy reforms and tackling management issues are considered to be important determinants of progress. For example, the lingering problems faced by health managers at all levels – insufficient coordination to provide integrated service, inadequate information about finance and costs to

improve efficiency, the problem of over- and under-utilisation of health services, and inadequate management of available human resources – remain unresolved. Even at that, efforts at finding the resources to achieve UHC are not very promising, especially in sub-Saharan Africa (SSA).

In April 2001, heads of state of African Union countries met in Abuja, Nigeria and pledged to a set target of allocating 15% of their annual budgets to improve the health sector. At that time, the median level of general government health expenditure from domestic resources from African Union Countries was very close to USD 10, with a thousand-fold difference between the minimum (USD 0.38) and the maximum (USD 380). Ten years after (2011), a report produced by WHO observed that while 27 countries increased the proportion of total government expenditures allocated to health, only Rwanda and South Africa achieved the 'Abuja Declaration' target of 'at least 15%'. Meanwhile, seven countries reduced their relative contributions of government expenditures to health during the same period, and there was no obvious trend upwards or downwards in 12 other coun-

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Dr Tarry Asoka is a seasoned consultant on health insurance in Nigeria. He thinks UHC can work, but cautions that it is going to require some creativity in the face of weak political will from governments



tries. But crucially, the report emphasised, 'the absolute level of resources available in relation to the health needs is well below what is needed'. And there are no signs whatsoever to suggest that things have changed much in the years following this report.

Other developments aimed at mobilising domestic resources for the health sector in SSA have not fared better either. A recent journal article published by *International Health* claims that 'social health insurance schemes in Africa leave out the poor'. Examining the proportion of women who delivered with assistance of a skilled health professional in relation to their wealth status, the paper demonstrated that in the five selected countries (Ghana, Tanzania, Kenya, Rwanda and Ethiopia) where national or community-based health insurance schemes exist; only Rwanda's poor seem to have almost the same level of access to a doctor/midwife, as the rich. Ghana, which for example has premium exemptions for pregnant women, has huge gaps in access: 'less than 50% of women in the poorest quintile deliver with the assistance of a skilled professional, compared with 97% in the richest quintile', the paper stated.

And in Nigeria, the richest country on the continent, three years after the national health law (National Health Act, No.8 of 2014) mandated the federal government to set aside at least 1% of the Consolidated Revenue Fund (CRF) to finance a Basic Health Care Package for all citizens, no funds have been released as no budgetary provisions have been made. There is news that some international donors in the country have put funds together to pilot what could be possible if 1% of the CRF is available to the health sector in 3 of its 36 states. What a paradox for an 'Africa Beyond Aid' plan that is being promoted by the current Ghanaian President, Nana Akufo-Addo. Yet, there may be opportunities that could propel African countries to make progress towards achieving UHC.

Beyond identifying workable health financing strategies and making them function properly within country-specific contexts, advances in development finance are worth exploring. Top on the list is 'Impact investment'. Structured like private equity funds in matured markets, these investment funds focus both on social impact and financial returns to investors (albeit modest), as well as paying annual fees to fund managers. In the health sector, supporting the set up of health insurance plans, providing access to essential medicines, developing

and maintaining provider networks, etc., that target poorer populations in both urban and rural areas are some projects considered agreeable to this concept. A related approach is 'Blended Finance', which aims to programme public (foreign government), philanthropic or development institution capital in such a way as to catalyse private investors to invest their capital in something they otherwise would not do. These could be infrastructural development in whatever form, but it would contribute to increasing access to health services in many ways. There is a sense that these ideas are becoming widespread among mainstream philanthropic foundations and donor agencies, in addition to commercial investors.

Other than looking for resources to finance UHC, what many observers are advising countries to direct their attention if optimising the health of their populations is the ultimate goal of UHC, is to look beyond the health system and begin to also address the social determinants of health. These may entail political programmes that include: better living standards, upgrading housing, improved nutrition, safe water and sanitation etc. Other actions could be related to tackling the rising prevalence of chronic diseases, such as cardiovascular diseases, diabetes and the rest through policies aimed at tobacco control, promoting healthy lifestyles and diets and so on.

Even within the health sector itself, it is suggested that actions intended to attain UHC could employ explicit priority interventions such as malaria control, maternal, newborn and child health care to drive the necessary improvements into the health system. Moreover, strong emphasis on district and community health systems where implementation and service delivery happens is vital, if a strengthened health system is seen as a necessary part of the toolbox to achieve UHC.

Despite these recommendations, the path or mechanisms for the realisation of UHC remains vague for many countries, in particular the nations in SSA. The *Lancet* alerts readers that in order to achieve the new 'health for all' programme through UHC, two misunderstandings must be appreciated. 'UHC is neither a destination to be reached nor a panacea for delivering better health, even in its broadest definition'. As progress is being made but slow, this should be a useful insight that could lessen the pain and frustrations of those clamouring for UHC nationally and globally.





# Health insurance is to be encouraged, but it won't bring the comprehensive coverage it promises

What does UHC mean, and is it attainable? And perhaps of particular interest given that this year heralds the 40th anniversary since the Alma Ata declaration, how does it vary from primary health care?

In simple terms, UHC is a healthcare system in which it is envisaged every citizen can receive health services without incurring financial hardship. Objectives include a strong, efficient, and well run health system; a means of financing the services (the critical bit); access to essential medicines and technology; and finally, a sufficient capacity of well-trained, motivated health workers.

Is it new? No it isn't. Norway is credited with being first with an UHC system back in 1913. Britain's NHS was launched in 1948 and is listed as being the sixth such system. So quite why it has suddenly come to the fore within the World Health Organisation agenda, isn't immediately clear.

But for sure there is some clear thinking behind it and hence its active promotion and adoption by groups such as the Africa Union Health Ministers. The premise is that investment in Africa's health systems is key to inclusive and sustainable growth.

Strong economic growth in recent years has helped reduce poverty to 43% of the population. Yet, as Africa's population expands – it is estimated to reach 2.5 billion by 2050 – the region faces a critical challenge of creating the foundations for long-term inclusive growth. Many countries still contend with high levels of child and maternal mortality, malnutrition is far too common, and most health systems are not able to deal effectively with epidemics and the growing burden of chronic diseases, such as diabetes. These challenges call for renewed commitments and (as WHO urges) the solution lies in accelerated progress towards UHC – the principle that everyone receives needed health services without financial hardship.

It is convenient to have a solution to point to. But can it work when finance remains the principal constraint in Africa? But the UHC proponents prefer not to dwell on such aspects at this stage. Much better to make the argument of why it is worth going the extra mile

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Bryan Pearson, editor of Africa Health, feels that too many will be left behind because by its very nature, health insurance is for the have's not the have not's. Better we should return to campaigning for the 15% of GDP promises of the Abuja declaration.

to try to make it work because there is a demonstrable benefit if it can be made to work: in other words, the investment will pay off.

The primary reason for investing in UHC is a moral one, they say: it is not acceptable that some members of society should face death, disability, ill health or impoverishment for reasons that could be addressed at limited cost. Who can argue with that? And strong health and disease surveillance systems also halt epidemics that take lives and disrupt economies. In 2015, the economic cost to the three Ebola-affected countries is said to be in excess of \$1billion. Who can decry avoiding such waste?

But while health expenditure in Africa has increased significantly, domestically financed government spending has stalled. Only four countries met the Abuja

Declaration target of 15% of government spending in 2016, and spending in almost 30 countries actually decreased.

Middle-income country health spending is growing, but largely due to the growing middle classes fuelling a welcome growth in private healthcare. Whilst positive, these groups still represent only a fraction of the population and the services they are accessing are not affordable to the majority of the popula-

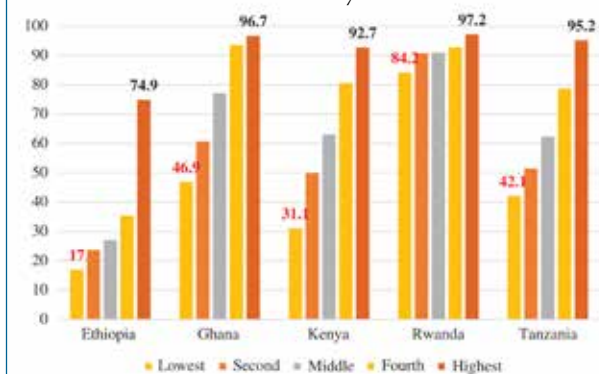
tions. The middle-income countries are also facing an additional challenge: they are losing the significant funding they have been receiving from groups such as the Global Fund and the immunisation specialists at GAVI. It is a tapered process, but it is truly challenging the gains made against many diseases as governments cannot easily suddenly replace the generous but necessary funding support that had been received previously.

But is UHC passing the buck? If governments committed the 15% of GDP as agreed in the Abuja Declaration, then there would not be the need for a largely insurance-based UHC system. Is it not surprising that the AU ministers voted for it, as it passes the onus for funding healthcare to the private sector or to national health insurance schemes? Primary Health Care was substantially similar in what it aimed to achieve (being the core base of the health pyramid) but it relied on public sector expenditure to make it work.

Doctor and nurse unemployment in Africa remains significant. Thousands of vacancies exist across all tiers of the health service, but funds are not available to finance them. Meanwhile there are influential groups like



*Proportion of women aged 15-49 who delivered with the assistance of a skilled health professional in five countries with national health insurance systems*



Source: DHS data for Ghana (2014), Kenya (2014), Rwanda (2014), Ethiopia (2011) and Tanzania (2015). From: *Int Health*. 2018;10(1):1-3. doi:10.1093/inthealth/ihx046

AMREF mounting campaigns for proper recognition of community health workers, including that they should be paid. Again, only the most mean-spirited ministry of official would disagree with the principle, but unless there is more money to spend in the MoH coffers, they are helpless to intervene.

Meanwhile many of the best doctors and nurses simply head overseas. Their training costs having largely been borne by their home country, but the benefits accrue to someone else.

This health workforce issue in fact goes much deeper. The shortages of appointed skilled health workers is a huge hindrance to the achievement of health targets. The estimated shortage of doctors, nurses, and midwives in WHO AFRO countries below the SDG Index threshold (4.45 physicians, nurses and midwives per 1000 population) was about 2.7 million in 2013. When all categories of health workers are included, the shortfall is estimated at 4.2 million. This total shortfall is expected to increase to 6.1 million in 2030. Shortages of health workers at the country level are exacerbated by severe imbalances in the density of skilled health workers: it is estimated that over 90% of pharmacists and dentists practice in urban areas, other cadres have similar distributions (World Health Organization 2016). Furthermore, accurate, updated, and nationally consistent information on health workforce is not always available, highlighting the need for strengthening essential countrywide information systems.

And yet this health workforce issue is also one of the most salient causes of the failure of PHC as envisaged in 1978. The workforce did not form the desired pyramid: with PHC at the base, District care at the centre, and Tertiary care at the top. PHC was introduced as a silo on its own. Doctors and nurses in the curative world, never properly bought in or became integrated with those working at the primary and preventive level. It is the same today in most places. Hence community health workers are expected to work voluntarily or for just very small amounts of cash, and it is rare to find them fully integrated into the larger health system. And yet it is human nature that you need leadership, mentoring, recognition

and support to work efficiently and effectively. PHC fractured from its lack of senior professional leadership.

Access to safe, affordable, and quality essential medicines and technologies remains a challenge. Despite progress in some areas, access to medicines in Africa remains low. The availability of selected medicines has been found to be as low as 21% in some instances, and weak pharmaceutical regulation, inadequate procurement and supply systems, limited access to information, all contribute to unnecessarily high prices and contribute to the dislocation of health delivery. Services become 'cash and carry' often with key medicines or consumables having to be bought from a local market. These conditions also contribute to the region having a significant circulation of counterfeit or falsified drugs. This all contributes to the gaps in access to essential HIV/AIDS, TB, and malaria services allowing them to remain as important barriers to achieving UHC in many countries.

Which brings us to the new nexus at the core of UHC: health insurance. Financial protection is generally low in Africa, requiring most patients to pay for health services from their own household income, so-called out-of-pocket (OOP) payments. Patients in low-income and lower-middle-income countries are less protected against high OOP than those in higher-middle-income countries. Out-of-pocket payments have increased in nearly all countries, and the regional average has increased from US\$15 per capita in 1995, to US\$38 in 2014. As a result, 11 million Africans are falling into poverty every year due to high out-of-pocket payments. Protecting people against the impoverishing effect of health payments is intended to become a cornerstone of UHC and a key driver to prevent poverty in Africa.

But is UHC too reliant on health insurance as the financial panacea? That is where I came in to this debate, and it is where I leave it? The history of health insurance in Africa is distinctly chequered, and distinctly mired in controversy. The public are highly suspicious (with good cause) of government agencies holding 'their' money; and owners of clinics and hospitals are equally nervous about having to wait inordinate amounts of time for reimbursement. That is not to say that some systems work well nor is it say that as time goes on it is going to become ever more important and relevant as a means of protecting the health of the individual or the family.

But the fundamental problem is that it doesn't tick the box of 'leaving no one behind', which is a key emotive call from those proposing UHC and its justification for being the new core policy. With a significant percentage of the workforce either in the informal sector or unemployed it almost by definition can't reach the poor. It thus isn't addressing the inequality it sets out to resolve. To me it is a bit like adopting the USA health system prior to Obamacare: if you can afford you can have, but if you can't you are on your own. Social health insurance is just not the right fiscal solution for Africa if your intention is to 'leave no one behind'. But maybe after years of fighting unsuccessfully for the Abuja declaration option, it is the best fallback option? But let us not dress it up as being the comprehensive solution it isn't.

# Harnessing technocrat skills to lead improved health delivery

Francis Omaswa on the trail of getting more from the talent we have



I want to return once again to our previous discussions on the potential contribution of our African Techno-professionals to Africa's transformation and to call upon this group to take our place as effective leaders wherever we are and at every turn. There is a critical mass of Techno-professionals in most African countries and our time is now.

This is inspired by two events taking place in East Africa. Along with my ACHESST colleagues, we attended the first event on 22 February, 2018 in Kampala. This was a Joint East African Community (EAC) Heads of State Retreat, where host President Y K Museveni of Uganda complained that the meeting room was too hot and apologised to his colleagues. He wondered what the engineers and technicians were doing if they are not able to keep the room comfortably cool. He also wondered what his protocol officers are doing – always walking up and down, looking busy without results. President Uhuru Kenyatta of Kenya followed by complaining about bureaucrats in his country who delay the approval and implementation of investment plans for up to two years. These engineers who could not keep the meeting room cool, the protocol officers and the Kenyan bureaucrats are all techno-professionals in whom we have placed great hope for the future. We will come back to discuss how to support this group at a later date.

The second event took place in mid April when we were represented at a meeting of Experts from EAC member states in Arusha, Tanzania. The challenge was to develop an implementation plan for the resolutions of the Heads of State Retreat in February 2018.

The Heads of State Retreat theme was 'Deepening and Widening Regional Integration through Infrastructure and Health Sector Development in the EAC Partner States'. With regard to health, the retreat sought to build consensus on regional health sector investment priorities for the attainment of Universal Health Coverage and the SDGs; showcase major health sector investments and opportunities in the region; mobilise new investments for the identified health sector priorities; and revitalise regional partnerships and linkages for improved health outcomes in the EAC. Non-health sectors' focus was on quicker delivery of priority projects in railways, ports, roads, inland waterways, energy and civil aviation sectors. All this effort, including the Heads of State retreat, is about agreeing Strategic Purchasing choices for a region with a total population of over 200 million people.

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

What principles should guide the identification of strategic purchasing priorities for the health sector? We recommend a more integrated public health approach that is not focused on addressing specific diseases. The investment priorities should revolve around the establishment of strong integrated primary and community health services and systems. This should be the foundation for ensuring that the disease priorities are addressed through health promotion, disease prevention and control with active participation of individuals, households and communities.

We call for concerted movement by EAC member states towards building health systems that work for everyone and are focused on integration of the investment priorities that are anchored within people-centred governance for services delivery across sectors that are household and community based and thereby leaving no one behind. 'Health is made at home and only repaired in health facilities when it breaks down'; 'If it does not happen in the community, it does not happen in the nation'.

We recommend institutionalisation of approaches on Continuous Improvement of Quality of Health Care (CQI), improved Health Sector efficiency and Health Sector statistics and disaggregated data sets. We propose investment in building capacity for Quality Assurance including planning, facilitative supervision, coaching and mentorship.

We advocate regular review and updating of service and performance standards and accreditation of facilities to be institutionalised in all member states.

We propose investment in health workforce plans that will provide the requisite skill sets and fit for purpose health workers where they are most needed.

There is sufficient evidence to show that the return on investment in health is high. EAC member states should allocate more funding from domestic sources for health. Member states should commit to a minimum per capita annual expenditure on health. On top of this, flexible and growing well-managed approaches to pooled funding through multiple mechanisms should be encouraged. These include community health insurance schemes moving towards compulsory national health insurance in combination with optional private health insurance schemes.

Strong stewardship, leadership, management and governance will be required to achieve the aspirations of this investment agenda. This calls for political commitment, strong support from techno-professionals and educated and informed demand from CSOs and communities.



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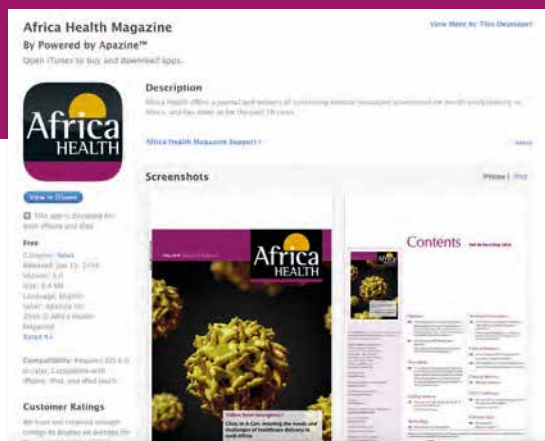
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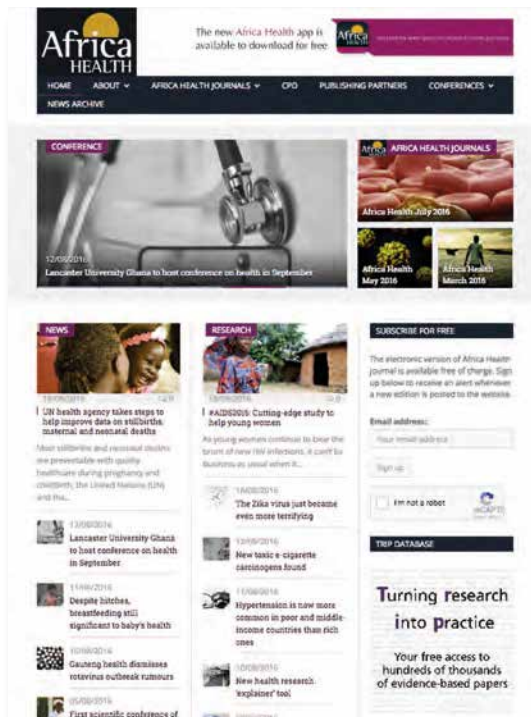
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# Shining a light on severe malaria

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.**

Join the community.  
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# Hospitals encouraged to be proactive on breastfeeding

WHO and UNICEF have issued a new ten-step guide to increase support for breastfeeding in health facilities that provide maternity and newborn services. Breastfeeding all babies for the first two years would save the lives of more than 820,000 children under five annually.

The Ten Steps to Successful Breastfeeding underpin the Baby-friendly Hospital Initiative, which both organisations launched in 1991. The practical guidance encourages new mothers to breastfeed and informs health workers how best to support breastfeeding.

Breastfeeding is vital to a child's lifelong health and reduces costs for health facilities, families, and governments. Breastfeeding within the first hour of birth protects newborn babies from infections and saves lives. Infants are at greater risk of death due to diarrhoea and other infections when they are breastfed only partially or not at all. Breastfeeding also improves IQ, school readiness and attendance, and is associated with higher income in adult life. It also reduces the risk of breast cancer in the mother.

'Breastfeeding saves lives. Its benefits help keep babies healthy in their first days and last will into adulthood,' says UNICEF Executive Director Henrietta H. Fore. 'But breastfeeding requires support, encouragement and guidance. With these basic steps, implemented properly, we can significantly improve breastfeeding rates around the world

and give children the best possible start in life.'

WHO Director-General Dr Tedros Adhanom Ghebreyesus says that in many hospitals and communities around the world, whether a child can be breastfed or not can make the difference between life and death, and whether a child will develop to reach his or her full potential.

'Hospitals are not there just to cure the ill. They are there to promote life and ensure people can thrive and live their lives to their full potential,' says Dr Tedros. 'As part of every country's drive to achieve universal health coverage, there is no better or more crucial place to start than by ensuring the Ten Steps to Successful Breastfeeding are the standard for care of mothers and their babies.'

The new guidance describes practical steps countries should take to protect, promote and support breastfeeding in facilities providing maternity and newborn services. They provide the immediate health system platform to help mothers initiate breastfeeding within the first hour and breastfeed exclusively for six months.

It describes how hospitals should have a written breastfeeding policy in place, staff competencies, and antenatal and post-birth care, including breastfeeding support for mothers. It also recommends limited use of breastmilk substitutes, rooming-in, responsive feeding, educating parents on the use of bottles and pacifiers, and support when mothers and babies are discharged from hospital.

## Audacious comes to Africa

Six countries in East and West Africa are shortly to become a part of a TED-sponsored project designed to fund 50,000 health workers to 'make a difference' in their communities.

The project started as a \$1million prize awarded to a Dr Raj Panjabi and his Last Mile Health agency, a non-profit that works with community health workers to expand healthcare access in remote areas. But the more he thought about it, the more he realised that he actually needed a lot more money. TED (the talk people) agreed with him, and after talking with a number of other foundations such as the Bill and Melinda Gates Foundation, the Dalio Foundation and the Skoll Foundation, a new programme was born. It is called the Audacious Project.

TED increased its funding to \$250 million, and with other contributions, they hope the final total will be somewhere north of \$600 million. Six groups (including Dr Panjabi's agency) were invited to bid. Other programmes were as diverse as a project for a methane-tracking satellite; and (through Sightsavers) a project to eliminate trachoma in less than a generation. Next year, access to the Audacious Project will be open for anyone to apply.

Last Mile Health has now teamed up with Living Goods, a non-profit also working with community health workers in Africa, to generate an even bigger plan. Community health workers trained through the programme will be equipped with smartphones loaded with an app to automate the diagnosis of deadly conditions. On top of that, the Academy platform will offer training videos to health workers so they can distinguish between life and death diseases (like severe and non-severe pneumonia).

'In reality, [Panjabi's] vision was much bigger than we could even support alone,' said Anna Verghese, the executive director of the Audacious Project and former head of the TED Prize. Under the auspices of the Audacious Project, Panjabi presented his plan to six undisclosed leaders in the business and philanthropy worlds, who will match up to \$50 million, dollar for dollar, of whatever he can raise.



## USA budget cuts threaten global disease security

The Trump administration is proposing huge budget cuts on the Centers for Disease Control (CDC) in Atlanta. If confirmed by Senate, the impact on international disease control programmes is going to be significant.

Despite clear evidence of the economic harm epidemics can wreak, the future upfront funding of the Global Health Security Agenda (GHS), a multilateral initiative to tackle global health threats, also remains uncertain as the American commitment waivers.

The CDC funding is perhaps the most critical. In perspective, its budget is triple that of WHO, and unless campaigners are successful in reversing at least some of the cuts, CDC has announced that it will have to reduce its epidemic prevention work in all but 10 of its 49 priority countries.

In parallel to this, global polio funding is also being wound down as eradication comes closer. Positive news indeed, but there is a sting in the tail. Currently almost 90% of WHO's lab and surveillance funding in Africa has come from polio money.

The cost of the West African ebola epidemic was in the region of \$3.6 billion with an economic cost the region of around \$2.8 billion. And this was just one epidemic. The economic impact of six major zoonotic disease outbreaks between 1997 and 2009 are thought to have cost more than \$80 billion globally.

## Genomic focus

As the genomics revolution finally turns its attention to Africa and northern researchers flock there to collect data, scientists from the continent are demanding a larger role in projects. A group of Africa-based researchers issued guidelines for the ethical handling of samples for genomic studies. The voluntary rules are an effort to combat 'helicopter' research and aim to ensure that African citizens see health benefits from the work done.

In recent years, researchers have begun sequencing the genomes of Africans in large numbers. The data offer insights into humanity's past as well as predisposition to disease and potential reactions to drugs in African populations – the world's most diverse genomically.

# Egyptian breakthrough in DNDi HepC treatment plan

An affordable hepatitis C treatment has been shown to be safe and effective, with very high cure rates for patients including hard-to-treat cases, in interim clinical trial results that offer hope to the 71 million people living with the disease worldwide.

The treatment is expected to cost \$300 for 12 weeks, or \$3.50 per day, in Malaysia, where trials were conducted along with Thailand – a fraction of the cost of other hepatitis C medicines produced by major manufacturers, which often run to tens of thousands of dollars.

The Drugs for Neglected Diseases Initiative (DNDi), a not-for-profit organisation, is working with the Egyptian drugmaker Pharco Pharmaceuticals to bring a combination treatment of two hepatitis C tablets, sofosbuvir – (a new drug) – and sofosbuvir, to countries that cannot afford to pay the high prices charged by US companies Gilead and AbbVie. This is taking longer than expected but has moved a big step closer with the latest Phase II and III trial results from tests with 301 patients. Funded by Médecins Sans Frontières, one of DNDi's founding partners that also include France's Institut Pasteur.

DNDi said 97% of patients were cured after being treated with the combination pill for 12 weeks. Even hard-to-treat cases such as people with HIV or liver cirrhosis showed very high cure rates, of 96% and 97% respectively.

Hepatitis C is a blood-borne viral infection that can lead to liver cirrhosis, cancer and death. It affects more than 71 million people worldwide and causes 400,000 deaths a year. Although highly effective medicines have been available for several years, their high cost means that less than three million people are on treatment.

US drug-maker Gilead has lowered the price of its Harvoni tablet and other medicines in lower and middle-income countries, but it is still too high for most governments to afford.

Harvoni now costs about \$48,000 for a 12-week course in Malaysia and

\$12,000 in Chile. Gilead's previous Sovaldi treatment cost \$1,000 a pill, or \$84,000 over 12 weeks. Prices vary around the world and tend to be highest in the US.



Gilead has come under pressure from US rival AbbVie, which launched a new hepatitis C medicine, Mavyret, last year with a shorter, eight-week treatment course priced at \$26,400.

Bernard Pécoul, executive director of DNDi, said: 'The results indicate that the sofosbuvir/ravidasvir combination is comparable to the very best hepatitis C therapies available today but it is priced affordably and could allow an alternative option in countries excluded from pharmaceutical company access programmes.'

The treatment is expected to be available in Malaysia within one to two years. DNDi has also signed deals in Latin America to make it available for \$500 for the 12-week course, with a provision to bring the price down to \$300.

The trial using medicines produced by Pharco was run by DNDi and co-sponsored by the Malaysian Ministry of Health.

The medicine has also been tested on 300 patients in Egypt, who have different genetic characteristics, with a 100% cure rate. Further studies are being carried out in South Africa and Ukraine to cover all six genotypes of the disease. DNDi has licensed rights for ravidasvir in low and middle income countries from the Californian firm that developed it, Presidio Pharmaceuticals.

# Immunisation funding gap as Nigeria transitions from GAVI

Bill Gates has called on Nigerians from all sectors to pull together to improve healthcare in the country, and in particular to improve immunisation rates. He and Nigerian billionaire Aliko Dangote recently met with various stakeholders and visited health facilities to see firsthand how services are being delivered.

For Nigeria to improve its health outcomes, particularly to end vaccine-preventable child deaths, the highest level of commitment and accountability from Nigerian leaders is imperative. While Gates told CNN that he wanted to spark action and debate during his visit, Nigeria leaders are the ones who need to respond with actual action of investing in health far beyond the current levels, starting with investing in immunisation.

As GDP has risen, so Nigeria has moved into the 'accelerated transition' phase of funding support from GAVI, the Global Vaccine Alliance, which means that its funding support for vaccination is being rapidly reduced and it will shortly be expected to start funding it itself. And yet Nigeria currently has the highest numbers of unimmunised children globally at over three million. In the past year alone, Nigeria has suffered outbreaks and tragic deaths from meningitis, measles, lassa fever, monkey pox and yellow fever. The Nigeria Centre for Disease Control has been playing a critical role in ensuring an increasingly rapid response to these outbreaks, but preventing them

in the first place should be the goal.

The reasons for the low immunisation rates are varied and include underlying factors like low awareness of the need for immunisation, poor parental understanding, and conflict-ravaged and fragile environments. An inequitable distribution of health workers, coupled to a weak health system also contributes significantly.

Unit costs for vaccination vary with hard to reach or remote areas often costing more than more accessible and high volume urban areas. Sadly, in Nigeria those not immunised are mostly the poorest people with less than 14% the poorest children between ages 12 to 23 months receiving pentavalent-3 vaccinations compared to 74.5% of the richest children.



Research shows that routine immunisation offers one of the highest returns on investments in health, saving up to 44 dollars in additional benefits for every dollar spent on routine immunisation, and allows children the chance to grow to be healthy and productive adults.

Several countries in Africa are now going through the transition process between receiving GAVI support and having to fund all the services themselves. It is a challenge that in this case brought two of the richest men in the world to plead for adequate public and private sector funding. The stakes are high if immunisation levels are allowed to drop.

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One in five children in Africa does not receive the vaccines they need.



It's time to accelerate action toward universal access to immunization in Africa.

## Getting serious with yellow fever

The UN is to lead an ambitious campaign to vaccinate nearly a billion people in Africa against yellow fever by 2026. Eliminating the mosquito-borne viral disease is the target. Yellow Fever has been a major killer on the continent as it spreads fast in highly populated areas with devastating consequences.

'With one injection we can protect a person for life against this dangerous pathogen' said Tedros Adhanom Ghebreyesus, Director-General of WHO at the programme's launch in Nigeria, a priority target country. 'This unprecedented commitment by countries will ensure that by 2026 Africa is free of yellow fever epidemics.'

'Today, the threat of yellow fever looms larger than ever before, especially for thousands of children across Africa,' Stefan Peterson, chief of health at UNICEF, said in a statement.

A major vaccination campaign in Angola and Congo in 2016 brought one of the worst outbreaks of the disease in decades under control after more than 400 people died. One reason the disease is spreading is because more people are moving from rural to urban areas.

'These areas tend to have high numbers of people living in close proximity with poor hygiene and sanitation – all the conditions that make it ripe for a disease outbreak,' he told the Thomson Reuters Foundation.

The vaccination programme is a joint venture by the WHO, UNICEF, the GAVI global vaccine alliance and more than 50 health partners.

## Commonwealth bonus

A special meeting convened by the Malaria Consortium on the eve of the Commonwealth Head of Government Meeting raised a landmark \$4.1bn commitment to continue the fight against malaria.

The Malaria Summit 2018, was hosted by the Governments of Rwanda, Swaziland and the United Kingdom, and was attended by His Royal Highness the Prince of Wales, Bill Gates, the Heads of State and Government and Ministers of 19 Commonwealth countries, as well as business leaders, philanthropists, scientists and civil society.



## Malaria: rocking or rolling back?

Professor William Brieger examines the Progress of malaria control in the forty years since the Alma Ata Declaration

The Concept of Primary Health Care (PHC) was formalised in 1978 when the World Health Organization and Unicef convened a major conference in the city of Alma Ata (now Almaty) in Kazakhstan.<sup>1</sup> The resulting Alma Ata Declaration resulted in advocacy for Health for All, which has evolved into Universal Health Coverage. The Declaration outlined important principles such as community participation in health care planning and delivery, promotion of scientifically sound and acceptable health interventions, the use of community-based health workers (CHWs), and addressing the common endemic health problems in each community. One of those endemic problems common to a majority of communities in Africa is malaria. Now, 40 years after the Alma Ata Declaration, we explore how malaria has progressed within the context of PHC.

### Roll Back Malaria also has an anniversary

The Roll Back Malaria Partnership (RBM) began in 1998, 20 years after Alma Ata. When RBM convened a meeting of African Heads of State in 2000, the resulting Abuja Declaration set targets for major malaria interventions of 80% coverage by 2010.<sup>2</sup> The Abuja Declaration reflected the principles of Alma Ata when it called on all member states to undertake health systems reforms to:

1. Promote community participation in joint ownership and control of Roll Back Malaria actions to enhance their sustainability.
2. Make diagnosis and treatment of malaria available as far peripherally as possible including home treatment.
3. Make appropriate treatment available and accessible to the poorest groups in the community.

By 2011, reality had intervened. WHO reported<sup>3</sup> that 'In the 10 years that has passed since the Abuja Declaration, there has been progress towards increasing the availability of financial resources for health at least in terms of dollar values. However, there has not been appreciable progress in terms of the commitments the Africa Union governments make to health, or in terms of the proportion of GNI the rich countries devote to Overseas Development Assistance.' Since that time, funding



from international and bilateral donors has levelled, such that there is even greater need for malaria-endemic countries to step forward and guarantee access to malaria prevention and treatment services are available through PHC at the grassroots. Such access needs to move beyond removing barriers to making malaria interventions attractive to the community.<sup>4</sup>

The actualisation of the Alma Ata approach to PHC requires investment. Atkinson et al. reviewed a variety of malaria interventions to learn whether efforts at global malaria elimination could benefit from PHC.<sup>5</sup> First they note that an elimination 'campaign calls for a health systems strengthening approach to provide an enabling environment for programmes in developing countries'. A traditional infrastructure and management approach will not realise the benefits of this (PHC) approach 'unless there is adequate investment in the 'people' component of health systems and understand

William R Brieger is a Professor for the Department of International Health, the Johns Hopkins Bloomberg School of Public Health, and Senior Malaria Specialist, Jhpiego, an affiliate of the Johns Hopkins University.

the multi-level factors that influence their participation'. They observed that a people-centered focus is needed in order that 'current global malaria elimination efforts do not derail renewed momentum towards the comprehensive primary health care approach.'

### The challenge of taking interventions to scale

Around this same time, James Christopher and colleagues examined how response to malaria and other childhood illnesses were faring 30 years since Alma Ata.<sup>6</sup> After reviewing seven studies of CHWs they concluded that 'CHWs in national programmes achieved large mortality reductions of 63% and 36% respectively when insecticide-treated nets and anti-malarial chemoprophylaxis were delivered, in addition to curative interventions.' They found little evidence of the effectiveness of these community interventions on pneumonia and diarrhoea. The challenge they saw was countries moving beyond successful studies to scale up and sustain community malaria control interventions to the national level and thereby reap the full promises and benefits of PHC.

More recently, Malaria Consortium has looked at the position of malaria control within the context of Community Based PHC (CBPHC) and the use of CHWs as a means for revisiting Health for All.<sup>7</sup> They define key community-based malaria activities including supporting mass drug administrations, mosquito net distribution, seasonal malaria chemoprevention, improving community knowledge of hygiene, sanitation and good health-seeking behaviour, and encouraging uptake of maternal services, such as antenatal care and intermittent preventive treatment of malaria in pregnancy (IPTp). Their report documents that community interventions avert many more child deaths than health facility based services. While noting that CBPHC has great potential, the authors also explain that this will not be attained unless, 'National governments...invest in national CBPHC programmes, but also have an important role in coordinating the various actors delivering CBPHC to ensure synergy rather than fragmentation.'

Ghana's community-based health planning and services (CHPS) programme aims to make primary care accessible at the grass roots. CHPS compounds are small clinics in space usually donated by the community, staffed by community health officers who oversee community-based agents (CBAs) and other community volunteers. Ferrer and co-researchers studied the effectiveness of this system in reaching children in the community who had malaria, pneumonia and/or diarrhoea.<sup>8</sup> Generally the community was satisfied with enhanced access to health services, and home-based care through CBAs increased prompt access to care. Unfortunately there were medicine shortages and inappropriate treatment problems. Better monitoring, supervision and logistical support is needed for such community systems fulfil the ideals of Alma Ata.

### Community based, not community owned

Questions have been raised as to whether the seeming strengths of CBPHA and CHW interventions for malaria and other endemic diseases are actually in keeping



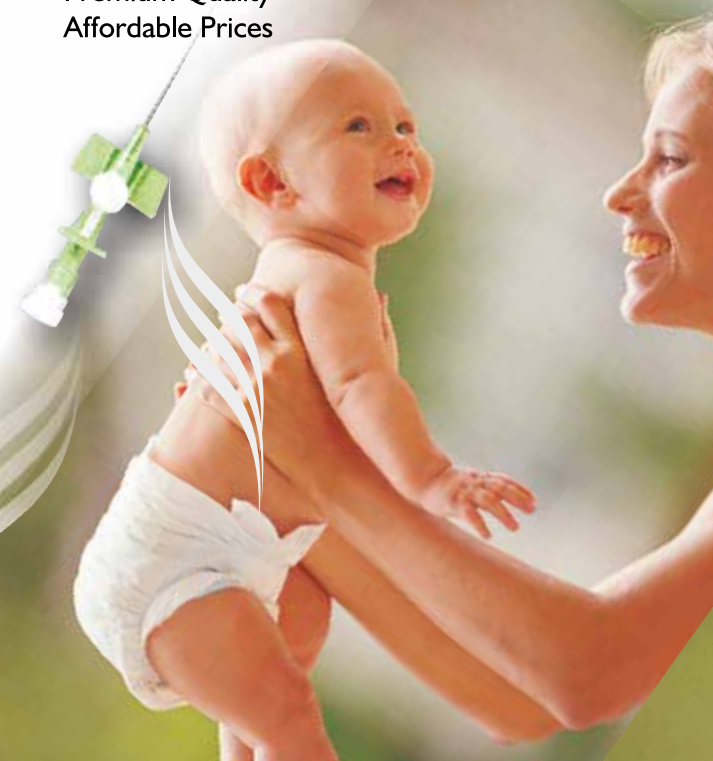
with the philosophy and goals of Alma Ata. Druetz et al.<sup>9</sup> look at the upsurge of interest in CHWs in low- and middle-income countries and the World Health Organization's global call to re-establish PHC policy as a 're-framing of this approach rather than its renewal'. Rather than promoting social change and community empowerment, these commentators wonder whether, 'Community case management of malaria perfectly illustrates this shift towards a pragmatic, medically centered, use of CHWs.' In short, 'By conceptualizing CHWs as front-line clinicians rather than as agents of social change, the case management of malaria becomes flawed.'

Along the way another disease control program, the African Program for Onchocerciasis Control (APOC) raised similar concerns. After multi-country community research, APOC arrived at an approach and policy known as Community-Directed Treatment with Ivermectin (CDTI).<sup>10</sup> CDTI was a community decision-making process that selected and oversaw local volunteers, conducted a village census and planned annual ivermectin distributions. Subsequently, another multi-country intervention study found that the CDTI approach could also successfully handle malaria community case management, community-led distribution of insecticide treated bednets and vitamin A provision, and in a couple settings directly observed treatment of tuberculosis. Through this approach, which became more broadly known as Community Directed Intervention (CDI), the community achieved success not by relying on one volunteer CHW, but by actively planning and distributing the tasks among its members.<sup>11</sup> Ironically, a single disease control programme led the way back to a more comprehensive delivery of essential health services through the community's own efforts.<sup>12</sup>

USAID's Maternal and Child Survival Program frames the context for malaria and other interventions clearly in the light of a re-envisioned PHC effort 40 years on:<sup>13</sup>

*2018 will see the 40 anniversary of the Alma Ata Conference. Though important successes have been achieved in increasing access to health, there is much work to be done. Years of vertical, horizontal, diagonal approaches to primary health care have not yet been successful in providing a fair chance for all women and children to thrive and transform their communities and societies. Are we ready to lead a paradigm shift in health systems thinking? Has*

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*the time finally come for building robust community health systems– supported by empowered and engaged communities – as a foundation of effective health systems?*

### Re-invigorating the PHC Approach

For now international donors will play an important role in ensuring malaria interventions reach the grassroots through community PHC efforts. The Global Fund to Fight AIDS, TB and Malaria (GFATM) has fostered the concept of community systems strengthening (CSS) as a supportive component to its basic disease control grants. CSS for Malaria<sup>14</sup> is 'A community-owned response is built on the principle of putting people first and on the belief that people have the capacity to respond, to take charge, to learn from each other, and to change.' CSS stresses community capacity building and a deep understanding of community structures, perceptions, gender and power dynamics, and the ways by which the community mobilises itself, among other components of a 'community system.' For malaria, CSS leads to ...

*Community-owned responses can potentially establish effective, sustainable links between available commodities, information about these commodities, and community members. Community-owned response can result in improved management of the local environment and efforts to promote appropriate health-seeking behavior, such as organizing transportation for complicated cases. Communities can also take a more active role in demand creation, influencing service provision (by monitoring local need), and regulating the activities of service providers, whether community-based volunteers, traditional healers, private sector vendors or health workers. Community-owned response approaches should, therefore, be used to complement conventional methods of communication and behavior change programming and service delivery.*

Controlling and eventually eliminating malaria will certainly go a long way toward helping achieve Health for All. On this 40th Anniversary year of Alma Ata, it is time to ensure that all malaria-endemic countries and malaria donors revisit the basic philosophy of community action and participation and ensure that these principals guide us to accessible and sustainable malaria programming by the community 'through their full participation'.

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# Misunderstanding seizures

## Challenges and steps to improving the diagnosis and management of people with epilepsy in sub-Saharan Africa

Epilepsy is one of the commonest *non-communicable* neurological disorders and an important cause of disability and mortality, affecting almost 70 million people worldwide. It is characterised by an enduring predisposition to generate epileptic seizures and by the ensuing cognitive, psychological, and sometimes severe social consequences. Here, we shall briefly look through the magnitude of the problem and the pertinent reasons for the vast treatment gap that exists in the resource-limited sub-Saharan countries, introduce the recent classification of the epilepsies by the International League Against Epilepsy (ILAE) and examine its relevance and pragmatic use as a tool in Africa, and finally suggest possible practical ways to improve diagnosis and management of people with epilepsy (PwE) through education and training.

### A synopsis of the problem

The prevalence of epilepsy (the proportion of PwE in the population at a given time) is higher in developing countries,<sup>1</sup> where 80% of PwE worldwide reside. In sub-Saharan Africa the prevalence varies widely between and within countries: notwithstanding methodological heterogeneity (for instance in terms of epilepsy definition and the ways of case ascertainment), and the varying incidence of risk factors, the median prevalence is much higher than in developed countries (14.2 per 1,000 vs. 5.8 per 1,000).<sup>2</sup> Yet, sub-Saharan countries are amongst the least equipped to deal with the complex diagnostic and therapeutic challenges because of poverty, illiteracy, and poor and unevenly distributed infrastructure and financial, human and material resources in the health sector. Under-nutrition, poor sanitation, spread of vectors of disease, endemic risk factors such as perinatal injuries and head trauma, and the increasing impact of HIV infection promote epilepsy. On the other hand, the substantial social stigma hampers access to PwE, while cultural beliefs that are negative about “western” anti-epileptic drug (AED) treatment (when this becomes available) and lack of knowledge about side effects and time to response are amongst the factors that affect compliance. On the other hand, insufficient knowledge about appropriate maintenance dosage of prescribed AED and the need of taking them regularly often leads

to under-treatment (Figures 1 and 2). These problems are more augmented in rural areas where most PwE reside and access to health facilities and follow up are difficult. Nearly all neurologists practice in large cities or suburban areas where also (video) EEG and MRI are available mainly in the private sector.<sup>3-5</sup> As a result, most PwE who reach out for treatment are looked after by primary-care physicians who have little or no specific training in epilepsy diagnosis and management and practically no access to EEG and brain imaging given the long waits when the latter are available in the public sector. Limited or non-availability and increased cost of AEDs is a major obstacle to the care of PwE, partly related to low profitability of agents like Phenobarbitone.<sup>6</sup> As a composite dismal result, the “epilepsy treatment gap”, defined as the proportion of people with epilepsy who require treatment but do not receive it, is enormous, reaching 95-100% in some rural areas of Tanzania, Nigeria, Uganda and Ethiopia.<sup>7</sup>

In contrast to the developed countries where, after a first peak in childhood, the prevalence of epilepsy peaks again in advanced age, the vast majority of the PwE in sub-Saharan Africa are younger than 20 years of age, reaching 80-90% in some areas. Compared to other non-communicable chronic diseases, such as diabetes and cardiovascular disorders, that peak at later stages of life and are not associated with stigma, epilepsy is a largely treatable condition with about 2/3 of patients achieving seizure control with AED in developed countries.<sup>8</sup> It is therefore more likely that, once the many complex challenges posed by epilepsy are successfully met, younger people will return to social life as fully contributing members.<sup>6</sup>

### Diagnosis of epilepsy and an update on the ILAE classification

Diagnosis of epilepsy is essentially clinical, based on skilful history and examination, and reliable information provided by witnesses. Once paroxysmal imitators of epileptic seizures, such as reflex convulsive syncope and psychogenic non-epileptic seizures<sup>9</sup> are ruled out, diagnosis of the clinical type and identification of the underlying cause are mandatory for appropriate management and treatment. The accuracy of the diagnosis of the epilepsy type is decisively assisted by the EEG, while the recognition of aetiology typically requires brain imaging and other laboratory investigations.<sup>10</sup> The new ILAE classification of the epilepsies<sup>11</sup> provides an orderly diagnostic process through three steps (levels) of increasing complexity to adapt to the available resources. The first step is the diagnosis of seizure type (of

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focal, generalised or unknown onset). It is important to emphasise here that generalised convulsive seizures can be truly generalised in their onset (called generalised tonic-clonic – GTC) or can have focal onset and evolve into otherwise similar generalised convulsions (called focal to bilateral tonic clonic); here a focal onset is not always clinically obvious (Figure 1). Non-convulsive seizures include focal and generalised that are clinically different to GTC, such as myoclonic and absences;<sup>12</sup> these seizure types can be difficult to clinically detect. The second step is the diagnosis of the epilepsy type (focal, generalised, combined focal and generalised and unknown), according to the seizure or combination of seizures it manifests with. The third level is the diagnosis of the particular epilepsy syndrome. At each one of these three levels of clinical diagnosis identification of the underlying cause should be promptly pursued.<sup>11</sup>

Ideally, AED selection should be based on the type of epilepsy and the individual circumstances and needs. Phenobarbitone has been deemed as the front-line AED,<sup>6</sup> mainly due to its low cost compared to other agents and its relatively wide-spectrum action. Although treatment with Phenobarbitone is better than no treatment at all (Figure 2), other AED can be more efficacious in several epilepsy types and syndromes. Beyond its usefulness in the treatment of the individual person with epilepsy, and because of its adaptability, the ILAE classification framework is also an effective tool for epidemiological studies that will help us better understand the multiple aetiologies of epilepsy and their contribution. The highly probable clinical under-diagnosis of focal epilepsies provides a good example.<sup>13</sup> With only a few exceptions, which found a higher representation of focal seizures,<sup>14-15</sup> most studies in sub-Saharan Africa have shown predominance of convulsive seizures and by implication of “active convulsive epilepsy” (ACE) when it comes to epilepsy type diagnosis.

EEG machines exist in most African countries<sup>16</sup> but many may be sub-optimally used or in the very-low-income countries often badly maintained or out of order<sup>3</sup> due to lack of trained personnel to maintain hardware and interpret registrations. Further, there are no governmental or professional authorities to ensure quality control, and no minimum standards exist for EEG laboratories.<sup>17</sup> Technologists and paramedical personnel have no formal training in EEG recording, physicians trained to basic EEG interpretation are few and relevant educational guidelines are lacking.<sup>18</sup> Incorrectly performed and reported EEGs not only deprive clinical assessment from an invaluable diagnostic tool, but may also result in over-diagnosis of epilepsy (for instance by inducing artefacts misread as epileptic discharges), incurring needless AED treatment that is hardly affordable. Further, inappropriate referrals exhaust the already limited capability of the few EEG labs prolonging waiting times for those who really need the test.<sup>19</sup> For instance, EEG is not necessary when a focal onset for generalised convulsions is clinically obvious (Figure 1) or can be deduced by history taking, or when PNES are strongly suspected, but is useful after a first seizure, for reclassification of ACE or the diagnosis of non-convulsive seizures or status epilepticus.



*Figure 1: If you don't have the money, you should save. This 32-year-old woman fell from a mango tree when she was 11 years old. One branch went through her skull right frontal. The surgeon in a rural hospital in Central Tanzania removed the branch, since when she suffered focal and generalised seizures. She was started on phenobarbital 30mg, an infant dosage of the only anti-*

*epileptic drug available locally. A CT brainscan was requested, but with medication barely possible from the family budget a scan was out of the question. Last year she came to our clinic with her sister and brought with her a 13-year-old request for a CT brainscan. She had spent years inside her house because the dosage of anti-epileptic medication had never been raised. Upon examination, there was a subtle left pyramidal weakness and normal intelligence. The skull had a clearly visible depression in the right frontal region, indicating where the epilepsy comes from. We decided the indication for CT scan had long expired. The first step, however, is an adult dosage of anti-epileptic drug treatment. If only we could have seen her before. Recently we saw her again, proudly having travelled alone from Central Tanzania. And seizure free.*

### Where do we go from here?

From the practical clinical standpoint, training of local physicians and other health professionals is an absolute priority, recognised by the ILAE as one of its primary goals.<sup>20</sup> Major conferences organised under the auspices of the ILAE offer regular teaching sessions, but attendance may be impossible for the many who have no financial support. Most will never have heard of such educational opportunities in the first place, having no access to internet or scientific journals or websites. Smaller-scale conferences and informal workshops at a more local level and with free participation could concentrate on important clinical, EEG and specialist nursing aspects and help groups of concerned health professionals to develop their interests and expertise, fostering a feeling of ownership of care. In particular, dedicated specialist nursing teaching<sup>21</sup> can focus on the education of patients and their families in how to manage their condition independently, keep self-safe and maintain follow up and trust, with emphasis on





*Figure 2: A lifelong breakthrough seizure. This 23-year-old accountancy student came into our clinic with his mother. He was born in our centre, and brought in his own file. When handing the file to us, it felt suspiciously thin. It turned out to be time travel: the unscathed, 23-year-old file only reported about the man's birth, mild birth asphyxia and convulsions, for which he was started on phenobarbital 30 mg, an infant dosage. Since then, he developed very well but kept having seizures. In the local dispensary on the sugar cane plantation where he grew up, medication had been refilled many times since. However, the dosage was never increased. Upon examination, he had no abnormalities on neurological examination except vivid reflexes, and a bit of a lisp. The explanation was that he had bitten off several chunks of tongue in the meantime. We tripled his dosage and he became seizure free.*

women with epilepsy during pre-conception, pregnancy, delivery and beyond. Epilepsy nurses can help with the development of important liaisons with other social groups, such as teachers, traditional healers and community leaders who hold key roles in the primary care frontline. Finally, practical (hands-on) training sessions on EEG recording would benefit health workers who could take up the key role of the EEG technologist to ensure correct recordings.

Concurrent with small-scale face-to-face teaching, educational articles and books can be used as practical tools of wider reach. A clinical-EEG diagnostic tool for clinical practice in adult<sup>22</sup> and paediatric<sup>23</sup> epileptology was recently prepared by the ILAE Neurophysiology Task Force, and can be freely downloaded. An open access, clinically practical tool can be modelled on this work, adapted to the pragmatic needs and limited resources that exist in sub-Saharan Africa, and enriched with chapters on management and treatment pitfalls, specialist epilepsy nursing and EEG basic principles and technology skills.

We believe such a publication would usefully complement the existing comprehensive text book on Neurology in Africa (Figure 3).<sup>10</sup>

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# NEPAD seeks champions

The New Economic Partnership for African Development (NEPAD) is looking for experts around Africa to join it in moving the African Medicines Regulation agenda forward

The African Medicines Regulatory Harmonisation (AMRH) Programme aims to improve access to medicines through harmonisation of regulatory requirements to ensure quality, safe and efficacious medicines are available to African citizens. It is a framework which provides an enabling regulatory environment for pharmaceutical sector development in Africa by promoting the harmonisation of medicines regulation among African countries through Regional Economic Communities (RECs), Regional Health Organisations (RHOs) and National Medicines Regulatory Authorities (NMRAs).

NEPAD Agency and its AMRH Partners are supporting RECs, RHOs and their member states in reviewing medicines regulatory policies, structures and systems and strengthening legal and institutional frameworks for effective medicines regulation. This is demonstrated by the increased use of harmonised policies and regulatory frameworks by member states, increased human and institutional capacity for regulation of medical products and technologies, and improved regulatory standards and practices through knowledge generation and shared learning.

As part of its strategy to strengthen medical products regulatory capacity, the AMRH Programme is in the process of establishing the AMRH Partnership Platform (APP). The partnership platform is intended to serve as a robust coordination mechanism to enhance efficiency and effectiveness in the implementation of the medical products regulatory systems strengthening and harmonisation agenda in Africa, through optimal coordination of the different partners and stakeholders providing regulatory support on the continent.

The establishment of the AMRH Partnership Platform aligns with the direction the World Health Organization (WHO) is undertaking and serves as the African-chapter of the WHO-Coalition of Interested Partners (CIP). This is a collective multi-stakeholder mechanism with a continent-wide common perspective to ensure that

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Interested? If you require more information on the above subject, please visit the AMRH Programme on the NEPAD website [www.nepad.org](http://www.nepad.org) or email all inquiries to [nancyn@nepad.org](mailto:nancyn@nepad.org) or call Nancy Ngum at +27 11 256 3557.

Applications should clearly state the scope of functions and/or category of product/s applied for together with comprehensive supporting documentation on meeting the eligibility criteria outlined.

All applications with supporting documentation should be addressed to: Margareth Ndomondo-SigondaHead, Health Programmes, African Union-NEPAD Planning and Coordinating Agency: Email: [margarets@nepad.org](mailto:margarets@nepad.org) and copy to [nancyn@nepad.org](mailto:nancyn@nepad.org)

partners build on progress made in the implementation of AMRH and various regulatory systems strengthening programmes and harmonisation initiatives.

Strategically, the AMRH PP is expected to: (a) increase collaboration among stakeholders supporting regulatory systems development in Africa; (b) foster mutual responsibility, accountability and shared impact; and ultimately; (c) minimise duplication; and (d) coordinate efforts at all levels of implementation of the medical products regulatory work in Africa.

Partners investing in different thematic areas of medical products regulatory systems strengthening and harmonisation will be identified and categorised in the following thematic areas: (a) dossier review and registration; (b) GMP inspections; (c) pharmacovigilance; (d) clinical trials; (e) post-marketing surveillance; (f) quality control and quality assurance; (g) medical devices & diagnostics; (h) blood and blood products; (i) policy and regulatory reforms; (j) regulatory capacity building; (k) other.

Members shall be institutions or representative of any other legal entity namely; organisations, companies or corporations that share the same goals, principles and values of jointly advancing the medical product regulatory systems strengthening and harmonisation agenda across the African Continent.

Members shall be drawn from the following groupings; intergovernmental organisations, funders/donors, pharmaceutical industry, civil society organisations (CSOs), research and academic institutions and private sector among others.

The following shall constitute requirements for consideration as an AMRH Partner: (a) members shall be ready to comply with the operating principles of the platform (Refer to the Accountability Framework for AMRH Stakeholders); (b) clearly defined statement of roles and responsibilities towards achieving the AMRH overall goal in line with identified and agreed thematic areas of support e.g. technical, financial or policy advocacy; (c) willingness to align and harmonise efforts with like-minded partners in order to avoid duplication and ensure clarity; (d) a duly completed expression of interest form indicating the area of interest, competency and existing expertise will be filled by members intending to join the AMRH Partnership Platform.

The selection process for becoming an AMRH Partner will include the assessment of submitted expression of interest forms. Organisations or individuals selected will expect to be monitored for continued performance based on agreed targets and metrics.

# Nosocomial infections and infection control

David R Jenkins

## Abstract

Nosocomial infections are a leading cause of avoidable harm in hospital patients and a substantial, unnecessary drain on healthcare resources. They are frequently caused by bacteria that are resistant to multiple antibiotics, and the treatment of nosocomial infections contributes to the selection of resistant bacteria. Understanding the complex interplay of factors that contribute to nosocomial infection is a necessary first step to improving patient outcomes. This article highlights the role of pathogens, patients, practice and place in both aetiology and management of nosocomial infections, and references additional reading for more detailed information.

**Keywords** Antibacterial drug resistance; *Clostridium difficile*; disease outbreaks; infection control; methicillin-resistant *Staphylococcus aureus*; MRCP; nosocomial infections; patient care bundles; surgical wound infection

## Defining nosocomial infections

Nosocomial (from the Latin *nosocomium* meaning hospital) infections are infections in hospital inpatients that were neither present nor incubating at the time of the patient's admission to hospital. Because of the difficulty of assessing the presence of an incubating infection, a practical approach is to define any bacterial infection as nosocomial if it becomes apparent >48–72 hours after admission. Viral infections with well-defined incubation periods can be more readily ascribed to community or nosocomial onset.

## The epidemiology of nosocomial infections

Nosocomial infections occur frequently. A point prevalence survey of 231,459 patients from 947 acute care hospitals across 30 European countries in 2011/12 revealed that, at any given time, 5.7% of patients had at least one nosocomial infection.<sup>1</sup> Patients of all ages and clinical specialties are affected by nosocomial infections, as are all anatomical sites (Table 1).

## The consequences of nosocomial infections

Nosocomial infections can be fatal or cause delayed recovery, functional impairment or aesthetic damage that can have life-long consequences for patients. Management of these infections often requires prolonged inpatient stay, additional investigations,

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## Key points

- Nosocomial infections are a major cause of harm for hospital patients
- Many infections can be prevented by good infection control practice
- Understanding the four main contributory factors — pathogen, patient, practice and place — helps with effective infection prevention

surgical intervention and antimicrobial treatment, all of which add to healthcare costs.

Across the world, healthcare payers are increasingly refusing to pay for the treatment costs of healthcare infections, claiming they could have been avoided. Hospitals in England are liable to lose the entire payment for an inpatient episode complicated by an avoidable nosocomial bloodstream infection with methicillin-resistant *Staphylococcus aureus* (MRSA). Healthcare regulators increasingly see nosocomial infections as preventable, and view rates of infection as a marker of the general quality of healthcare delivered by an organization.

## Antimicrobial resistance

Nosocomial infections are an important factor in the emergence and spread of multidrug-resistant (MDR) bacteria. Broad-spectrum antibiotics, such as vancomycin, third-generation cephalosporins and carbapenems, are often used for empirical treatment of infected patients, thereby selecting for and favouring the persistence of MDR pathogens.

Defined terms are used to describe the extent of resistance. MDR organisms are resistant to at least one agent in three or more antimicrobial categories. Extensive drug resistance (XDR) is resistance to at least one agent in all but two or fewer antimicrobial categories. Pan-drug resistance (PDR) is resistance to all agents in all antimicrobial categories.

Important MDR causes of nosocomial infections include MRSA, vancomycin-resistant enterococci (VRE) and MDR Gram-negative bacilli, particularly *Escherichia coli* and *Klebsiella* species. The development of carbapenem resistance in Gram-negative bacteria, through the emergence of various carbapenemase genes, is increasing the prevalence of infections caused by XDR and PDR pathogens, and threatening the ability to deliver safe healthcare in many countries. Nosocomial infections caused by resistant fungi are also increasingly reported. The developing resistance crisis is worsened by a lack of new antibiotic classes entering clinical practice.

## Infection prevention

### The 'four Ps' of infection prevention — pathogens, patients, practice and place

Prevention is the best approach to management of nosocomial infections and can be addressed by considering the interaction of pathogens and patients within the context of clinical practice in the place where healthcare is delivered (Figure 1).



### Relative frequency of nosocomial infections and causative organisms in a point-prevalence survey across Europe, 2011/12, in 13,829 infected patients

Infection type	Relative percentage of all nosocomial infections	Most frequent causative organisms (percentage of cases caused by identified pathogen)
Pneumonia	19.4	<i>Pseudomonas aeruginosa</i> : 17.4
Other lower respiratory tract infections	4.1	<i>Staphylococcus aureus</i> : 12.6
		<i>Klebsiella</i> spp.: 11.4
Surgical site infections	19.6	<i>Staphylococcus aureus</i> : 17.9
		<i>Enterococcus</i> spp.: 14.5
		<i>Escherichia coli</i> : 14.0
Urinary tract infections	19.0	<i>Escherichia coli</i> : 36.2
		<i>Enterococcus</i> spp.: 12.5
		<i>Klebsiella</i> spp.: 12.0
Bloodstream infections	10.6	Coagulase-negative staphylococci: 18.5 <sup>a</sup>
		<i>Staphylococcus aureus</i> : 15.9
		<i>Escherichia coli</i> : 11.0
		<i>Klebsiella</i> spp.: 9.8
Catheter-related infections without bloodstream infection	1.6	
Cardiovascular system infections	1.4	
Gastrointestinal system infections	7.6	<i>Clostridium difficile</i> : 48
Skin and soft tissue infections	4.0	
Bone and joint infections	1.6	
Central nervous system infections	0.6	
Eye, ear, nose or mouth infection	3.0	
Reproductive tract infections	0.6	
Systemic infections	6.2	
Other/unknown	0.8	

<sup>a</sup> Coagulase-negative staphylococci are a frequent contaminant of blood cultures, but are genuine pathogens in many device-related nosocomial bloodstream infections.

Data source: European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European hospitals 2011–2012 (2013).

**Table 1**

**Pathogens:** the range of infecting microorganisms extends from prion proteins (Creutzfeldt–Jakob disease (CJD) and variant CJD), through viruses, bacteria and fungi to parasites and arthropods such as the scabies mite.

The most frequently isolated pathogens in the European survey are shown in Table 1. Many are normal members of the human microbiota – the thousands of microbial species found naturally on the epithelial surfaces of the skin, oropharynx and gastrointestinal and genitourinary tracts. These, along with less frequently isolated microorganisms such as *Acinetobacter baumannii*, *Serratia* species, *Stenotrophomonas maltophilia* and *Aspergillus* species, are important because of their propensity for cross-infection and their ready ability to acquire resistance to multiple antimicrobials.

Certain subspecies of bacteria, characterized by the possession of genes for virulence markers or antimicrobial resistance, have emerged as significant causes of nosocomial infection that can spread on an intercontinental scale. MRSA infections in England in the early 2000s were mostly caused by just two strains, epidemic MRSA 15 and 16. A global epidemic of *Clostridium*

*difficile* infection, peaking in England in 2007, was caused by a single strain, the 027 ribotype. Its spread was facilitated by antibiotic resistance, particularly to fluoroquinolones, and by a gene variant responsible for raised levels of toxin production. This modified gene led to severe diarrhoea and contamination of ward environments with high numbers of *C. difficile* spores, with increased numbers of secondary cases.

**Patients:** important patient determinants of infection risk include:

- extremes of age
- poor nutritional state
- obesity
- diabetes mellitus, lung, liver or renal disease, malignancy or immunodeficiency
- smoking
- coexisting infections.

Patients requiring emergency surgery are at increased risk of infection relative to elective patients undergoing the same procedure.

## The 'four Ps' of healthcare infection prevention

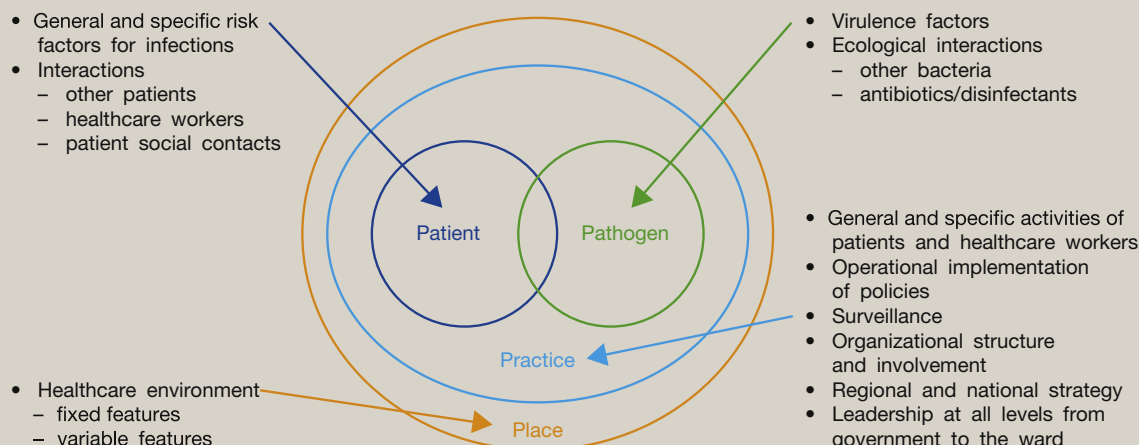


Figure 1

## The pathogen–patient interaction (Figure 2):

*Translocation* – most nosocomial infections are caused by the affected patient's own microbiota moving from its natural site to the site of subsequent infection, often because of medical or surgical procedures. Examples include:

- surgical site infections caused by skin bacteria, especially *S. aureus*, introduced into the surgical wound at or soon after surgery
- catheter-associated urinary tract infections caused by Enterobacteriaceae (coliforms), such as *E. coli*, introduced into the bladder from the urethra during catheterization
- respiratory infections caused by the patient's oropharyngeal bacteria, including *Streptococcus pneumoniae*, entering the lower respiratory tract as a consequence of impaired coordination of swallowing, decreased conscious level, endotracheal intubation or respiratory toileting.

*Patient-to-patient transmission* – pathogens can be transmitted directly between patients through:

- direct contact (e.g. MRSA, VRE, MDR Enterobacteriaceae)
- respiratory route:
  - droplets (e.g. influenza, respiratory syncytial virus)
  - aerosols (e.g. varicella zoster, pertussis, tuberculosis).

Alternatively, transmission can be indirect, for example:

- by transfer of MRSA via a healthcare worker with suboptimal hand hygiene
- through the shared use of contaminated medical devices
- from shedding of pathogens into the clinical environment and acquisition by a subsequent patient (e.g. norovirus, *C. difficile*).

*Healthcare workers as a source of infection* – infected and colonized healthcare workers are a risk to patients. Potential threats include surgeons with blood-borne viruses (e.g. HIV, hepatitis B and C) and ward staff with respiratory (e.g. influenza, pertussis, tuberculosis) or skin (e.g. herpetic whitlows) infections.

*Infections from the environment* – airborne spores of environmental fungi, such as *Aspergillus* species, are a particular risk to immunocompromised patients. Hospital water distribution systems are vulnerable to colonization by *Legionella pneumophila* and *Pseudomonas aeruginosa*. Contaminated water used

## Routes of acquisition of nosocomial infections

1. Infection from index patient's own microbiota
2. Direct patient transmission
3. Indirect patient to patient transmission
4. Transmission from healthcare worker (HCW)
5. Transmission from environment

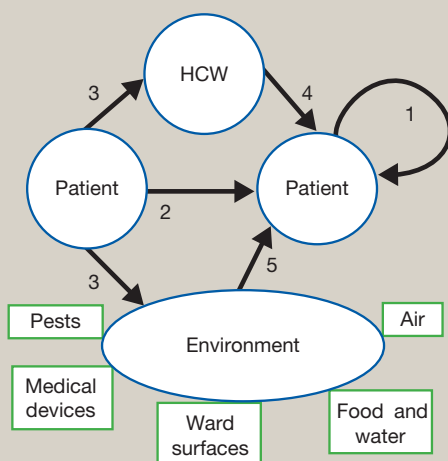


Figure 2

for drinking or washing can cause infection with these and similar environmental organisms in susceptible patients. Patients with impaired swallowing reflexes, lung disease or immunosuppression are vulnerable to Legionnaires' pneumonia. Premature neonates, intubated patients on intensive care units and burns patients are particularly susceptible to respiratory and bloodstream infection with *P. aeruginosa*. Contaminated food and water can lead to gastroenteritis by food poisoning bacteria (e.g. *Salmonella*, *Campylobacter*, *E. coli* 0157) and viruses (e.g. norovirus).

*Medical devices as a source of infection* – reusable medical devices, including surgical instruments and endoscopes, should undergo stringent decontamination to ensure safety for subsequent patients. Modern sterilization processes virtually guarantee the elimination of viruses, bacteria (including bacterial spores) and fungi from surgical instruments, but contamination with CJD prion protein remains a risk, at least theoretically.

Reusable endoscopes present a decontamination challenge. These heat-sensitive instruments cannot be sterilized using autoclaves; instead, they undergo high-level decontamination with disinfectants. These noxious chemicals have to be rinsed off with water, which presents the possibility of recontamination with waterborne organisms including *P. aeruginosa* and environmental mycobacterial species, causing both genuine and pseudo-infections. Environmental mycobacteria can cause disease in susceptible patients, including individuals with cystic fibrosis. They can also mimic the appearance of *Mycobacterium tuberculosis* during the laboratory microscopic examination of bronchoalveolar lavage specimens, falsely implying the patient has tuberculosis.

*Mycobacterium chimaera infection – an example of a new threat* – since 2011, there has been a growing number of reports of endocarditis caused by this slow-growing mycobacterium in patients who had undergone cardiac surgery months to years earlier.

Contaminated water in the reservoirs of heater–cooler units used during bypass surgery has been identified as the source. Pumps in the heater–cooler units generate infectious aerosols that settle in the operative site and develop into infection. Whole-genome sequencing of *M. chimaera* isolates from patients and from the heater–cooler factory indicates that the heater–cooler units were probably contaminated during manufacture. *M. chimaera* infection following cardiac surgery has a high mortality rate: of 30 UK cases so far, 16 patients have died.

**Practice:** many nosocomial infections can be prevented by good infection prevention policies and practice. The frequent use of the hands in delivering healthcare underscores the critical importance of hand hygiene in infection prevention.

A recent systematic review from the World Health Organization (WHO) found convincing evidence that improvements in hand hygiene practice lead to reductions in transmission, colonization and infection by MDR bacteria.<sup>2</sup> The WHO promotes a hand hygiene programme, *My 5 Moments for Hand Hygiene* (before touching a patient, before clean/aseptic procedures, after body fluid exposure/risk, after touching a patient, after touching patient surroundings), recommending the use of alcohol-based hand rub as the routine method of hand decontamination.

*Infection prevention care bundles* – modern infection prevention approaches advocate the simultaneous implementation of multiple coordinated interventions. Compendia of evidence-based interventions have been published by a number of national bodies.

The Department of Health document, *epic3: National Evidence-Based Guidelines for Preventing Healthcare-Associated Infections in NHS Hospitals in England*, provides recommendations covering the areas of hospital environmental hygiene, hand hygiene, use of personal protective equipment (PPE), safe use and disposal of sharps, and principles of asepsis.<sup>3</sup> The Society for Healthcare Epidemiology of America and Infectious Diseases Society of America have published joint infection prevention guidelines, the latest of which addresses catheter-associated urinary tract infections, *C. difficile*, surgical site infections, central line-associated bloodstream infections, MRSA transmission and infection, ventilator-associated pneumonia and hand hygiene.<sup>4</sup>

Infection prevention practice themes include the following:

- **Prevent introduction of pathogens to the healthcare environment and patients** (e.g. identify patients who pose a cross-infection risk because of MDR carriage, respiratory infection, infectious diarrhoea or blood-borne viruses, through patient history, examination and microbiological screens; isolation of infectious patients, pre-admission antiseptic body washes, occupational health screens to identify infectious staff, staff vaccination).
- **Maintain a clean clinical environment** (e.g. ensure routine cleaning meets approved standards, use enhanced methods such as hydrogen peroxide vapour to decontaminate wards following occupation by patients carrying resistant or virulent organisms, monitor hospital water microbiological quality for *Legionella* and *Pseudomonas* species, ensure good food hygiene standards).
- **Prevent translocation of bacteria to potential sites of infection** (e.g. avoid use, or limit duration, of intravascular devices and urinary catheters, use patient skin disinfection before insertion of intravascular devices and surgery, use aseptic non-touch techniques for sterile procedures, use appropriate perioperative antibiotic prophylaxis, use non-invasive ventilation if possible, or endotracheal tubes with subglottic secretion drainage ports and selective oral decontamination in intubated intensive care patients).
- **Train staff** in awareness of high-risk patients and situations, appropriate use of isolation facilities and PPE, and appropriate antibiotic-prescribing strategies.
- **Monitor and improve processes and outcomes** through policy and guidelines development, audit and surveillance.

**Place:** the place where healthcare is delivered is usually a fixed element in hospital care but plays an important role in nosocomial infections. Ward design (e.g. number of beds, space between beds, availability of single-occupancy rooms, toilets and wash hand basins, adjacencies of services, ventilation and water distribution systems) and choice of furnishings and furniture contribute to the transmissibility of pathogens, the ability of staff to practise good infection control precautions and the ease of environmental cleaning. Best practice guidance on designing and



building healthcare buildings to prevent infections is available from the English Department of Health.<sup>5</sup> ◆

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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

## Paediatrics

### Neonatal sepsis

Estimates of the global burden of neonatal sepsis, especially in low- and middle-income countries (LMIC) are scarce. This is owing to a number of reasons including the large proportion of infants born at home, limited facilities for diagnosis and with restricted resources priority is given to treatment of older infants and children.

A retrospective review of hospital-based childhood deaths was undertaken in Malawi, where the under-5-mortality rate is 64/1000 live births. The major causes of death were malaria 26.0%, malnutrition 13.6%, HIV-related illness 9.9%, sepsis 8.9% and perinatal deaths 4.4% (perhaps a third of which may have been due to sepsis).<sup>1</sup> Deaths in the neonatal nursery were excluded. The study demonstrates that in this setting priority for detection and managing neonatal sepsis is dwarfed by the burden of disease in older infants and children.

In a review of 150 newborns clinically suspected of sepsis in Ghana, the median (IQR) gestational age was 38 weeks (36-39) and 26 (17.3%) had positive blood cultures. All were resistant to ampicillin.<sup>2</sup>

A prospective study of neonates born in three tertiary care centres in Delhi, India enrolled 13,530 infants of 88,633 live births (15.3%) suspected of sepsis between 2011 and 2014.<sup>3</sup> The total incidence of sepsis was 14.3% and of culture-positive sepsis was 6.2%. Two thirds of the total episodes occurred at or before 72h of life (early onset sepsis, EOS). Multidrug resistance was defined as Gram-negative isolates resistant to three of five antibiotic classes (extended-spectrum cephalosporins, carbapenems, aminoglycosides, fluoroquinolones and piperacillin-tazobactam). Two-thirds of 1005 isolates were Gram-negative and multidrug resistance was detected in 38-82%. Methicillin resistance (MRSA) was found in 61% (85/140) of coagulase-negative staphylococci and 38% (43/114) of *S.aureus* isolates. Nearly a quarter of deaths were owing to sepsis.

A literature search of antimicrobial resistance in LMIC from 1990-2008 found 10 relevant reports.<sup>4</sup> Resistance against *E.coli* was as follows: ampicillin 72%, cotrimoxazole 78%, third generation cephalosporins 19% and gentamicin 13%. The first-line antimicrobial agents recommended by WHO for serious infections in young infants is ampicillin and gentamicin.

Most of the detailed research on neonatal sepsis is undertaken in high-income countries (HIC) which have

among other tools the benefit of good microbiology services and antimicrobial stewardship, meticulous records and data collection, PCR in addition to optimal practices in obtaining cultures of body fluids, and a range of inflammatory markers. However, the downside is the relatively large proportion of very low birth weight (VLBW) infants requiring often prolonged mechanical ventilation, intravenous and enteral feeding and exposure to multiple invasive devices which are often complicated by systemic fungal infections.

In a report of almost 400,000 live births at academic-based neonatal centres in the USA between 2006 and 2009, there were 389 infants with EOS (0.98 cases per 1000 births) with 43% due to *Streptococcus agalactiae* (GBS) (0.41 per 1000 live births) and 29% to *E.coli* (0.28 per 1000 live births).<sup>5</sup> Most infants with GBS infections were full term (73%) and 81% of those with *E.coli* were preterm. Overall case fatality was 16% and it was inversely related to gestational age: 54% at 22-24w, 30% at 25-28w, 12% at 29-33w and 3% in infants more than 37w gestation. Mortality rates for infants with GBS were 9% and were 33% with *E.coli* sepsis. However, when adjusted for gestational age, mortality rates were similar. Although GBS is isolated from infants (and their mothers) in LMIC<sup>6</sup> it is uncommon. This might be partly due to laboratory difficulties in differentiating GBS from other streptococci. Intrapartum antimicrobial prophylaxis administered to GBS-colonised women has reduced the prevalence of early GBS invasive infections and Gram-negative pathogens are now emerging as an increasing cause of EOS.<sup>5</sup>

Low maternal and neonatal vitamin D levels are associated with increased risk of EOS.<sup>7</sup>

In HIC coagulase-negative staphylococci (CONS) are the most common isolates in late-onset sepsis (LOS), followed by *S.aureus*, a proportion of which are multiresistant (MRSA).<sup>5</sup> However, the prevalence of CONS can be substantially reduced by good infection control measures.<sup>8</sup> *Candida* spp are now the third most common cause of LOS in LBW infants (<1500g). Apart from prematurity, gastrointestinal colonisation and vascular catheterisation are important risk factors which, if reduced, have the potential for control of fungal transmission.<sup>5</sup>

The key to diagnosis of neonatal sepsis is the ability to repeat blood and CSF cultures and indices of inflammation. Up to a third of VLBW infants may have meningitis but no signs of systemic sepsis.<sup>9</sup> Inflammatory indices include total leucocyte count (WBC) and differential, ratio of immature/total neutrophil ratio (I/T),<sup>10</sup> C-reactive protein (CRP),<sup>11</sup> ESR and procalcitonin levels.<sup>12</sup> WBC should be estimated after 4h of age and due to the varying levels during the first 12h of life serial measurements are more informative than a single one. CRP requires hepatic synthesis after the onset of infection and thus serial measurements, if possible in combination with other acute phase reactants and markers such as procalcitonin and interleukins levels (e.g. 6 and 8), are required. Procalcitonin levels may also be used in decisions to reduce antibiotic therapy in neonates suspected of EOS.<sup>12</sup>

In LMIC it is estimated that rates of neonatal sepsis in the community are up to 170/1000 live births when

clinically diagnosed and 5.5/1000 live births when diagnosed by blood culture.<sup>13</sup> In many regions of LMIC the majority of births take place at home or in first-level health facilities, and even if sepsis is diagnosed, access to hospital may be constrained for a number of reasons, including availability of transport. It is essential that management of neonatal sepsis should commence in the community with adequate training of health workers and availability of appropriate antibiotics. In the hospital environment it is not known (nor may never be known) how many infants with neonatal sepsis die because of the very serious increasing evidence of multidrug resistance to first and second (and even third) line antimicrobials. There must be increased awareness of the risk of sepsis, especially EOS, and regular availability of inflammatory markers, e.g. WBC and differential and CRP. Stewardship of antimicrobials has to begin in both the community and health facilities.

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## STIs

### Syndromic management of STIs

Syndromic management of sexually transmitted diseases based on a patient's symptoms remains an important, low-cost tool for diagnosing and treating infections in many low resource settings worldwide. The accuracy of

these syndromic approaches, however, often depends on how well the syndromic protocol corresponds with the prevalence of infections and levels of antibiotic resistance in the local population. National protocols must be regularly updated to reflect these evolving factors, and health care providers must receive training on the revised protocols. While syndromic management can be very effective, there are many situations where it performs poorly.

A systematic review of syndromic management of vaginal discharge culled through 2,845 studies and evaluated 16 of these which used the WHO Vaginal Discharge Flowchart<sup>1</sup> and found the diagnostic flowcharts performed poorly at identifying cervical infections (*Neisseria gonorrhoeae* and *Chlamydia trachomatis*).<sup>2</sup> The four flowcharts had sensitivity (among those with infection, what percent test positive) of 27.37%. The flowcharts were more successful at identifying vaginal infections (Bacterial vaginosis and *Trichomonas vaginalis*). Based on these findings, the authors conclude the vaginal discharge flowcharts should focus on management of vaginal infections, and they could be used an intermediate approach for cervical infections among sex workers. Another systematic review of abnormal vaginal discharge flowcharts assessed 36 studies and 99 flowcharts.<sup>3</sup> Summary sensitivities for WHO flowcharts ranged from 41.2 to 43.6%, and for locally adapted flowcharts from 39.5 to 74.8%. Overall the flowcharts were found to be poor diagnostic tools, with many women receiving unnecessary treatment and many women with cervical infections were not detected.

A study in Zimbabwe assessed the aetiology of symptomatic vaginal discharge and the adequacy of the current syndromic management guidelines.<sup>4</sup> Of the 200 symptomatic women in the study, 146 had an aetiology detected, including bacterial vaginosis (24.7%), *N. gonorrhoeae* (24.0%), yeast infection (20.7%), *T. vaginalis* (19.0%), *C. trachomatis* (14.0%), and *M. genitalium* (7.0%). The syndromic management protocol covered 115 (57.5%) of the women who had gonorrhoea, chlamydia, *M. genitalium* or bacterial vaginosis, while 85 women (42.5%) received treatment without a diagnosis.

Syndromic management is more successful among men presenting with urethral discharge. Men presenting with urethral discharge in Zimbabwe are treated with a single intramuscular dose of kanamycin or ceftriaxone in combination with a week's course of oral doxycycline. A study of 200 men with urethral discharge in Zimbabwe found 163 (81.5%) had one or more pathogens, including *N. gonorrhoeae* (73.5%), *C. trachomatis* (22.5%), *T. vaginalis* (4.0%) and *M. genitalium* (3.5%) (5). Among these men, 60% had one infection, 20% had two infections, and 1% had three infections. The current syndromic management and treatment protocols are adequate, but ongoing monitoring for gonococcal resistance is needed.

Another analysis from the Zimbabwe STI Etiology Study assessed how well the syndromic protocols for genital ulcer disease (GUD) performed (6). Of the 200 men and women in the study, 38.5% were positive for Herpes simplex virus (HSV), 16% positive for *T. pallidum* (syphilis), 1% positive for Lymphogranuloma venereum (LGV)-associated strains of *C. trachomatis*,



and 49% had no infection. For all GUD patients, HIV positivity was 52.2%, with higher rates among women (59.8 % vs. 45.2% among men) and among patients with HSV (68.6% vs. 41.8%). There was a high rate of chlamydia and gonorrhoea comorbidity (31% of women and 23.5% of men). However, 63% of women and men with coinfections (17% of all patients with GUD in this study) did not have vaginal or urethral discharge, and would have not received treatment under syndromic protocols. Future guidelines should address these coinfections.

A study in South Africa highlights the risks of missed STI infections. Two-hundred and ninety-eight HIV-sero-negative females, ages 16-22, from Soweto and Cape Town were tested for STIs and bacterial vaginosis (BV).<sup>7</sup> The study found rates of BV (46.6%) and HPV (66.8%) were high in both communities. Rates of infection with *C. trachomatis* and *N. gonorrhoeae* were more than twice as high in Cape Town than in Soweto (chlamydia: 42% vs. 18%; gonorrhoeae 11% vs. 5%). Only 24% of the adolescents with vaginal discharge-causing STIs or BV were symptomatic. In this group, syndromic management of vaginal discharge had a sensitivity of 23% and specificity (among those without infection, what percent test negative) of 85% for diagnosing a discharge-causing STI or BV. More than 70% of the young women in this study with treatable STIs that could enhance HIV risk would have been missed by syndromic management alone.

### Point of care testing

One of the best ways to improve on syndromic management of STIs is to use point of care (POC) tests to confirm infection and enable effective treatment in one visit. Fortunately, there are many highly sensitive and specific tests now available to test for *C. trachomatis*, *N. gonorrhoeae*, and *T. vaginalis* and the technologies are changing rapidly. A systematic review of 33 research studies on POC tests for these pathogens found at least one test for each infection with sensitivity and specificity  $\geq 90\%$ .<sup>8</sup> There is need for more research on the acceptability, feasibility, cost, and sensitivity and specificity among populations not considered to be at risk, including pregnant women.

The December 2017 Supplement to the journal *Sexually Transmitted Infections* focuses on POC testing for STIs and includes reviews of the performance of POC tests for dual tests for HIV and syphilis, urogenital gonococcal infections, urogenital *Chlamydia trachomatis*, *Trichomonas vaginalis*, and human papillomavirus.<sup>9</sup> It also includes reports on the evaluation of POC tests for syphilis in Brazil, and among men who have sex with men in Verona, Italy; on the acceptability and feasibility of scale-up of dual HIV/syphilis testing in Malawi; and POC tests that combine diagnostics with antimicrobial resistance prediction for *N. gonorrhoeae* and *M. genitalium*.

Recognising the importance of POC testing in the overall strategy to address the impact of STIs on global health, the World Health Organization Department of Reproductive Health and Research convened a group of experts in 2014 and 2015 to develop protocols for independent evaluation of promising POC tests, to

investigate implementing these core protocols in select countries, and to develop a roadmap for the development of new POC tests.<sup>10</sup> While there are many diagnostic products in the pipeline, there is need to help these along by setting up evaluation sites, harmonising regulatory processes, and modelling cost-effectiveness.

### STI challenges

The journal *Lancet Infectious Diseases* published a comprehensive Commission on STIs in July 2017 which discusses recent advances in STIs and promotes debate on the education, control, treatment, and diagnosis of STIs.<sup>11</sup> Based on input from international experts, the Commission identified five areas where there have been significant advances, new problems have emerged, or the epidemiology of infections has changed. These areas are: future directions of the control of chlamydia, treatment of gonorrhoea in the face of increasing antimicrobial resistance, cause of bacterial vaginosis and implications for treatment, challenges in the diagnosis and control of STIs in low- and middle-income countries, and how the medical interventions to address HIV infection might affect other STIs. Three other challenges of importance, but not included in the Commission are also discussed: the control of *M. genitalium*; the burden of syphilis, with a focus on China; and what improvements in the management of STIs should be implemented at the health system level.

### Non-traditional STIs

There are more than 30 recognised sexually transmitted infections worldwide, including those transmitted primarily by sexual contact and those that can be transmitted sexually, but whose primary mode of transmission is by food, vector or droplet.<sup>12</sup> The latter types of non-traditional STIs pose significant challenges to health care providers. One study looked at shigellosis and *N. meningitidis*, two infections that have recently emerged as sexually transmissible.<sup>13</sup> Shigellosis is a diarrhoeal disease caused by the species of bacterium *Shigella*. Once most common in children and international travellers, in the 1970s the infection grew more common among men who have sex with men (MSM) in the United States. Sexual transmission of *Shigella* likely occurs during oral-anal or digital-anal sex. Routine case reporting for *Shigella* does not include information about sexual practices, but rising rates of *Shigella* among men in the US and England between 2004 and 2015, while rates declined among women and children, indicate *Shigella* is re-emerging as an STI among MSM. Some *Shigella* strains are showing multidrug resistance internationally among MSM.

*N. meningitidis* is the bacterium that causes invasive meningococcal disease (IMD). It is spread primarily by droplet and infects the respiratory mucosa. About 5-10% of healthy adults are nasopharyngeal carriers, and the bacterium has also been isolated in men with urethritis. *N. meningitidis* in the human urogenital tract could be the result of oral-genital sexual contact, and the bacterium is genetically adapted to the urogenital tract. More recently there have been outbreaks of IMD among MSM in Europe, Canada and the US. It is not clear what the primary mode of transmission is between MSM.

Two other viruses have been newly recognised as being sexually transmissible. In the Ebola virus outbreak

in West Africa in 2013, there were more than 28,000 confirmed cases and more than 11,000 deaths. Follow-up of cases among individuals not in close proximity to those infected led to the confirmation of Ebola virus in semen. While this had been confirmed in prior outbreaks of Ebola, in this outbreak, Ebola was found to persist in male semen 565 days after the onset of symptoms. Although the risk of transmission from semen is thought to be small, the number of male Ebola survivors made flare-ups a concern even as the epidemic declined. It is thought female-to-male transmission of Ebola is inefficient, but possible.

The large outbreak of Zika virus in Latin America and the Caribbean in 2015-2016 drew global attention in part because of its association with microcephaly. While the primary mode of transmission is through the bite of the *Aedes spp.* mosquito, sexual transmission of Zika has been confirmed since 2008. An estimated 80% of Zika infections are asymptomatic, creating a huge reservoir of virus.<sup>14</sup> Case reports from 13 countries now document probable sexual transmission, via oral, anal and vaginal sex, to partners of travellers returning from endemic areas. Like Ebola, Zika virus persists in the body. The maximum time the Zika virus has been confirmed to survive in genital fluids is 188 days in semen by reverse transcriptase PCR (RT-PCR), 69 days in semen by culture, 3 days in vaginal fluid by RT-PCR, and 11 days in cervical mucus by RT-PCR. These non-traditional STIs offer lessons for the future detection, prevention and control of other re-emerging and newly recognized STIs.

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## Pharmacy

### Falsified Medicines

I have written before about counterfeit medicines, and there is now more international interest. Europe is introducing on Saturday 9 February 2019, the Falsified Medicines Directive (FMD). Falsified is defined as contains no active ingredient, the wrong active ingredient or the wrong amount of the correct active ingredient. It does not include medicines that contain the correct amount of the active ingredient, but are labelled as a different brand.

The system will work be each individual container (pack or bottle) printed with a 2-D barcode identifying each pack (representing a 20 digit number). The *Pharmaceutical Journal*<sup>1</sup> describes the process as identifying each pack at the point of dispensing, then decommissioning (removing from the active database). The system ensures that the manufacturer also adds a tamper-proof seal to each container.

If a pack has a bar-code that doesn't match the manufacturer's information, or a duplicate barcode dispensing the pack is prohibited.

The cost of the system is funded by the manufacturers, but there are concerns that it would take longer to dispense the medicines, and that training is required.

This system appears to be the European solution similar to two systems reported by the BBC in 2016 ([www.bbc.co.uk/news/business-37470667](http://www.bbc.co.uk/news/business-37470667)). Both the mPedigree and the Sproxil system use a scratch-off label with a number that is sent by SMS and the database confirms if the pack is genuine.

All these systems have a unique pack identifier. If they are implemented on a larger scale they should reduce the amount of counterfeit medicines on sale.

### Pregnancy and Breast Feeding

Some of the more difficult enquiries concern the use of medicines in pregnancy and breast feeding. For many medicines there is no good information, and no one source provides sufficient details for all patients.

Recently the BNF (British National Formulary) has re-designed the layout in order to make it easier to read electronically. There used to be appendices about pregnancy and breast feeding; now the information is within each monograph. The information in the BNF is accurate, however it errs on the side of caution, and the information is not always useful for the immediate care of patients.

The BNF is available as an App for iPhone and Android, and online at [www.medicinescomplete.com](http://www.medicinescomplete.com), however access may be restricted in some countries.

## Hear Disease in Pregnancy and Breast Feeding

According to some sources, cardiovascular disease has overtaken infectious and insect-mediated disease in some parts of Sub-Saharan Africa,<sup>2</sup> and that cardiac disease (including pre-eclampsia) carry a very high mortality rate in pregnancy. The BMJ (*British Medical Journal*) published a review of cardiac medicines in pregnancy and breast feeding<sup>3</sup> with specific reference to pregnancy in women with congenital heart disease, although much of the information is useful to cardiac disease in general. The article includes a chart of the safety of many cardiac medicines in both pregnancy and breast feeding.<sup>4</sup> The key points of the article relate to pre-conception advice:

- Offer woman of childbearing age with cardiovascular disease counselling and risk stratification before conception
- Counselling is best made available within the paediatric cardiology transition service
- Offer the woman appropriate contraceptive advice
- In women contemplating pregnancy, change cardiovascular medications to those which can be used in pregnancy, and emphasise the importance of close monitoring
- In women not contemplating pregnancy, ensure effective discussion on contraception and early pregnancy termination

The article includes a table derived from the WHO<sup>5</sup> of the relative risks to the mother and infant of the various categories of cardiac disease in the mother.

Class I carries almost no risk, class IV including pulmonary arterial hypertension carries a severe risk of mortality to the mother.

The drugs considered to be safe both in pregnancy and breast feeding are:

- Beta-blockers: labetalol and bisoprolol
- Calcium channel blockers: nifedipine and atenolol
- Platelet inhibitors: low dose aspirin
- Anti-arrhythmic drugs: procainamide and flecainide
- Diuretics: furosemide and hydrochlorothiazide.

Drugs contraindicated in pregnancy are: ACE (angiotensin converting enzyme inhibitors, e.g., captopril), angiotensin receptor blockers (e.g., candesartan), spironolactone.

The chart is especially useful to prescribers and will be a standard reference where I currently work.

## Drug Errors

The Policy Research Unit in Economic Evaluation of Health & Care Interventions (EEPRU) has issued a major report of drug administration errors.<sup>6</sup> Error rates reported are up to 90%, but some reports have errors as low as 0.2%. A presentation at the East of England Global Health Conference<sup>2</sup> gave medication omission rates of 20%, which was not altered by applied interventions.

Most interventions (72%) are reported to cause no harm to the patient although some can cause death, mainly in elderly patients.

The most significant cause of death (up to 50% of total deaths) from adverse drug reactions (drug side effects) is gastro-intestinal (GI) bleeding cause by NSAIDS (non-steroidal anti-inflammatory drugs, e.g., ibuprofen, diclofenac), anticoagulants (e.g., warfarin), and anti-platelet drugs (including aspirin, and clopidogrel).

The risk of errors was highest in children, patients with renal (kidney) failure, and the elderly. Up to 7% of hospital admissions in the UK are due to side effects of medicines, about two-thirds of these could have been prevented. Prescribing errors varied between care settings. Errors in primary health care (General practice) were about 5%; in secondary care (Hospitals) about 1%; in care homes (mainly for the elderly) about 40%. Administration errors accounted for about 40%, and dispensing errors 16% of the errors. Adverse drug reactions and drug errors cost the NHS in England almost £100 million. Overall 2% of drug errors cause serious harm to patients, but 70% cause minimal harm to patients.

There are interventions that can be made to reduce errors in medication include alerts on high risk drugs. A systematic review identified 12 drug groups that account for 80% of hospital admissions that are medication-related and preventable. Three groups of drugs that are responsible for over a third of these admissions; anticoagulants, antiplatelets and non-steroidal anti-inflammatory drugs (which all cause gastrointestinal bleeding). An important implication from this study is that reducing hazardous prescribing in general practice associated with specific groups of drug could prevent the majority of medication-related hospital admissions.

An article in the *European Journal of Hospital Pharmacy*<sup>7</sup> looked at dispensing errors in the use of trade-names (rather than generic names, although some errors were caused by generic name confusion) for dispensing. The most common error overall was dispensing the wrong amount of drug, but over 40% of errors involved dispensing the wrong drug, and 9% involved the wrong strength of the drug. The overall incidence of dispensing errors was give as 0.02%.

Overall the conclusions could be that there is no substitute for reading and understanding the label on the medication.

## Medicines Information for All

A poster presentation<sup>8</sup> at the East of England Global Health Conference looked at the worldwide accessibility of information on medications. The research found that most information was received from the pharmaceutical industry. The amount of research on the subject was minimal (fewer than 50 articles), and that further research was needed.

Alistair Bolt, Pharmacist Practitioner

Norfolk and Norwich Univeristy Hospital, UK

## References

- 1 The Pharmaceutical Journal, February 2018, Vol 300, No 7910, online I DOI: 10.1211/PJ.2018.20204387
- 2 Conference presentation. East of England Global Health Conference. Robinson College Cambridge. March 14th 2018
- 3 Clinical Update Pregnancy in women with congenital heart disease BMJ 2018;360:k478
- 4 BMJ Visual Summary Using cardiovascular drugs during pregnancy. [http://www.bmj.com/content/bmj/suppl/2018/03/08/bmj.k478.DC3/pregnancy\\_heart\\_disease\\_v28\\_web.pdf](http://www.bmj.com/content/bmj/suppl/2018/03/08/bmj.k478.DC3/pregnancy_heart_disease_v28_web.pdf)
- 5 Modified World Health Organization classification of maternal cardiovascular risk. Adapted from Thorne et al, 2006 and Regitz-Zagrosek et al, 2011
- 6 Elliot RA et al. Prevalence and economic burden of medication errors in the NHS in England EEPRU Feb 2018. Available at <http://www.eepru.org.uk/wp-content/uploads/2018/02/medication-error-report-revised-final.2-22022018.pdf>
- 7 Tseng H-Y et al Dispensing errors from look-alike trade names, Eur J



(See page 40)

## One

Q1 (a) (b) (c) (d) (g). Answers (c) and (d) are crucial. You must not assume that her new pattern of headache (more frequent) is just a change in her migraine associated with pregnancy. The two may be unrelated, and you must rule out more serious causes of pregnancy-related headache regardless of her history of migraine. Answer e) is also vital as you may need to change her routine and her medication to protect the foetus (see answers to Q3).

## Two

Q2 (a) (b) (c) (d) (e). All of these answers should feature in her non-pharmaceutical management. Sudden stopping of all caffeine drinks may precipitate an attack, so if she is drinking an excess of them (say four or more cups of coffee a day) she could cut down on them slowly, but she does not have to avoid them completely.

## Three

Q3 (a) (b) and (c). Answers (d) and (e) are wrong. Low dose betablockers such as propranolol have recently been shown not to be linked to a higher risk of congenital anomalies. The same goes for low dose amitriptyline at night. The anti-emetics listed in (f) are all safe to use in pregnancy.

## Four

Q4 (a) (b) (c) (d) are all complications of pregnancy that are more frequent in migraine sufferers, and Mary should be aware of the need to recognise any early symptoms of them and to attend all her clinic appointments, where urine and blood pressure tests will pick up any early changes. Glaucoma is not a particular risk in migraine, and orthostatic headache (acute headache on changing posture) is a red flag for an impending stroke not necessarily linked to a migraine attack. It should be treated as an emergency in all pregnancies regardless of a history of migraine.

Mary sailed through her pregnancy: her headaches were tension headaches probably linked with anxiety. Once reassured, and given advice on how to deal with her anxiety, they disappeared. She was one of the lucky ones – her migraines diminished to almost nothing during her pregnancy.

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# Infection

## Existing vaccine linked with gonorrhoea incidence

Gonorrhoea is steadily becoming a global public health problem due to the combined effects of increasing antibiotic resistant strains and as-yet unsuccessful vaccine development. The disease is associated with significant morbidity and the development of effective management is well desired. Surveillance data has picked up a potential link between an existing vaccine and incidence of gonorrhoea. A retrospective case-control study conducted using individuals aged 15-30 years in New Zealand showed that exposure to three doses of the outer membrane vesicle meningococcal B vaccine (MenNZB) was associated with a reduced rate of gonorrhoea diagnosis. This is the first time a vaccination has been shown to impart any protection against the infection. Whilst producing differing disease manifestations, there is up to a 90% genetic homology between *Neisseria gonorrhoea* and *Neisseria meningitidis*, for which the vaccine was used against, and each share several equivalent virulence factors. This may provide biological backup for any link between vaccine exposure and decreased incidence of gonorrhoea. These findings encourage further research into the pathogenic factors that might be impacted by the vaccine.

Petousis-Harris H, Paynter J, Morgan J, et al. Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study. *Lancet* 2017; 390:1603-1610

## Brain imaging in congenital Zika syndrome

Following the 2015 outbreak of Zika virus in Brazil there is a growing population of children born with congenital Zika syndrome, the clinical course of which is not yet known. Early brain CT scans were performed on these children to assess for hydrocephalus. These scans have also demonstrated calcifications particularly present at the cortical-white matter junctions within the brain. One study has used follow up imaging to assess for changes in existing calcifications identified in 37 children with congenital Zika virus. The average time of initial scan was performed at 11 days of age followed up by repeat scan at an

average of 415 days of age. At follow-up, calcifications had diminished in size and number in 34 children. One scan had demonstrated complete resolution of calcifications and no change was seen in two scans. The improved calcification burden did not correlate with improvement of clinical signs. Detection or absence of calcifications may not be a useful tool in the late diagnosis of congenital Zika syndrome.

Petribu N, Aragao M, van der Linden V, et al. Follow-up brain imaging of 37 children with congenital Zika syndrome: case series study. *BMJ* 2017; 359 :j4188

## Persistence of Ebola virus in semen

Ebola virus is mainly transmitted via direct contact with blood or bodily fluids. With the presence of Ebola virus detected in the semen of men following recovery of Ebola, there has been concern about the risk of sexual transmission. There had been recommendations for Ebola survivors to abstain from sexual intercourse or use a condom for 3 months after recovery but these have been revised and lengthened following report of sexual transmission. A study has looked at semen samples from 220 male survivors of Ebola virus to assess duration of viral load in the semen by measuring Ebola virus RNA. Of this group 27% had positive initial samples. At 4 to 6 months the virus was detected in 62%, 25% with semen obtained at 7 to 9 months and 4% with a specimen taken from 16 to 18 months. Samples taken at 19 or more months were all negative for Ebola virus. The study did not directly evaluate risk of sexual transmission. Ebola virus may be present long-term in the semen of recovering men but declines with time.

Deen GF, Broutet N, Xu W, et al. Ebola RNA Persistence in Semen of Ebola Virus Disease Survivors — Final Report. *NEJM* 2017; 377:1428-1437

# Obs & Gyn

## Frozen versus fresh embryo transfer

For nonovulatory women with polycystic ovarian syndrome undergoing in vitro fertilisation (IVF), elective use of frozen-embryos has proven to be more successful than fresh-embryo transfer but it is uncertain if the same stands for ovulatory women. A trial involving over 2100 women with regular menses has set out to investigate this.

Participants undergoing their first IVF cycle were randomised to receive either fresh-embryo transfer or cryo-preservation of the embryo followed by frozen embryo-transfer. Between the two groups the live-birth rate outcomes did not differ significantly. There were also no between group differences in rates of implantation, clinical pregnancy, on-going pregnancy or overall pregnancy loss. However, the risk of ovarian hyperstimulation syndrome (OHSS) was significantly lower in the frozen-embryo transfer group. OHSS can result in severe abdominal pain, cause blood clotting in the legs and can even be fatal.

Shi Y, Sun Y, Hao C, et al. Transfer of Fresh versus Frozen Embryos in Ovulatory Women. *NEJM* 2018 ; 378:126-136

## Biomarkers of ovarian reserve in fertility prediction

Biomarkers indicating ovarian reserve are increasingly being promoted as a marker of fertility among women, despite a lack of evidence. A study has investigated if low levels of antimüllerian hormone (AMH), suggesting low ovarian reserve, can indeed act as a useful marker for infertility in women of late reproductive age. The study included 750 women aged 30 to 44 years who had been trying to conceive for 3 months with no history of infertility. Participants were followed up for the outcome of conception achieved by 12 attempted cycles. The study found that women with low AMH levels did not significantly differ in probability of conception outcome from women with normal values at 6 cycles of attempt. Predicted probability of conception was also not significantly different between women with high versus normal levels of follicle stimulating hormone. Inhibin B levels were also found to not be a useful marker for infertility in women. These findings do not support the use of these biomarkers of ovarian reserve to predict fertility in women of late reproductive age.

Steiner AZ, Pritchard D, Stanczyk FZ, et al. Association between biomarkers of ovarian reserve and infertility among older women of reproductive age. *JAMA*.2017;318(14):1367-1376. doi:10.1001/jama.2017.14588

## Breast cancer recurrence following endocrine therapy

Standard adjuvant management of early oestrogen-receptor (ER) positive breast cancer is a five-year course of endocrine therapy. Extending the duration of endocrine therapy does further

reduce risk of recurrence but it can have additional side effects. A meta-analysis has analysed the progress of 63,000 female ER-positive breast cancer patients from 88 trials to assess association of original tumour size and nodal status with risk of recurrence at 20 years. Patients included were cancer free at 5 years when adjuvant endocrine therapy was ended. In the fifteen-year period following adjuvant endocrine therapy distant breast cancer recurrence rates steadily rose and were associated with the original tumour size and nodal status. The risk of recurrence ranged from 13 to 41% according to tumour size, nodal status and tumour grade. The largest risk of recurrence was at 41% in women with large tumours that had spread to at least 4 lymph nodes. This research supports the use of further methods to reduce long term recurrence which may include extended endocrine therapy.

Pan H, Gray R, Braybrooke J, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. *NEJM* 2017; 377:1836-1846.

### Surveillance of cervical pre-invasive lesions

Cervical screening allows the early detection and intervention of pre-invasive and invasive lesions and subsequently there has been noticeable reduction in mortality from invasive cervical cancer. Largely, the pre-invasive and benign lesions are well characterised and understood, with clear management guidelines. In the middle of this non-invasive group is the classification known as cervical intraepithelial neoplasia 2 (CIN2) for which the natural course is not well understood. Either side of it sit histological classifications that have well described courses and as a result management protocols with CIN1 a benign diagnosis and CIN3 a true cancerous precursor. A meta-analysis has looked at the progression of CIN2 lesions managed conservatively for over 3 months. Using 36 studies that included over 3100 women, it was found that 50% of CIN2 lesions regressed, 32% persisted and 18% progressed. The authors argue that active surveillance women diagnosed with these lesions is justified, particularly among a young population who are likely to adhere to screening.

Tainio K, Athanasiou A, Tikkinen K et al. Clinical course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: systematic review and meta-analysis. *BMJ* 2018; 360 :k499

### Duration of lactation and diabetes

Glucose intolerance is fast becoming a global burden. It is important that we identify contributing factors and understand how we can manipulate the mechanisms involved to reduce the burden and the associated morbidity of diabetes. A protective association exists between lactation duration and diabetes. Previous studies have reported a reduced incidence of diabetes of between 3% and 15% per year of lactation. However, these studies have included older women and were based solely on self-reported diagnosis of diabetes. A study has now investigated if this protective link is biochemically supported. Data were taken from over 1,200 women in the Coronary Artery Risk Development in Young Adults (CARDIA) study which includes data spanning 30 years. Duration of lactation was strongly, and independently, associated with a lower incidence of diabetes with most benefit seen at the longest duration measured in the study of 12 or more months. Lactation duration is protective against development of diabetes.

Gunderson EP, Lewis CE, Lin Y, et al. Lactation Duration and Progression to Diabetes in Women Across the Childbearing Years: The 30-Year CARDIA Study. *JAMA Intern Med.* 2018; 178(3):328-337. doi:10.1001/jamainternmed.2017.7978

nal fluid (CSF) spaces but not following short duration missions. Three of the long duration group had optic-disc oedema on return, and all three had an MRI demonstrating a narrowed central sulcus. The clinical significance of these changes remains unclear.

Roberts DR, Albrecht MH, Collins HR, et al. Effects of spaceflight on astronaut brain structure as indicated on MRI. *NEJM* 2017; 377:1746-1753.

### Gene replacement therapy for muscular atrophy

The motor neuron disease 'spinal muscular atrophy' (SMA) is a severe childhood monogenic disorder that results in a failure to achieve motor milestones, need for ventilation, or death in young children. It is caused by loss or dysfunction of the gene encoding survival motor neuron 1 (SMN1). A study has looked at if single gene replacement therapy can benefit infants born with this disorder, primarily investigating safety of the technique. Motor milestones in infants who were given a single dose of therapy (n=15) were compared to historical cohorts. At 20-months of age all infants were still alive versus a survival rate of 8% in the historical cohort. Motor milestones, quantified by a scale of motor function, had improved at 3 months compared to a decline in the historical cohort. Results included infants able to sit unassisted, speak and two that could walk independently. A single intravenous infusion of adeno-associated viral vector containing DNA coding for SMN resulted in longer survival, superior achievement of motor milestones, and better motor function than in historical cohorts

Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. *NEJM* 2017; 377:1713-1722.

### Remyelinating therapy in MS

The disease process behind multiple sclerosis (MS) involves an inflammatory, autoimmune demyelination of the nerve cells of the central nervous system (CNS). This leads to dysfunction of neuronal transmission and the resultant symptoms of MS, including visual nerve dysfunction. Currently therapies target the inflammatory and immune mediated damage yet there are no effective treatments that address re-myelination. A double-blind randomised study has assessed safety and efficacy of using clemastine fumarate, an over the counter antihistamine that has been shown to stimulate the

## Neurology

### Brain structure following space flight

There have been reports of visual impairment and raised intracranial pressure in astronauts on return from space missions but the cause is not known and the effect of microgravity on the brain during space travel has not been extensively studied. An imaging study has now looked at the configuration of the brain following space flight in astronauts using MRI. Imaging was taken on return of astronauts from missions of both long (average 164 days) and short duration (average 13 days), and compared with previous imaging. In 17 of the 18 astronauts who had been on long duration flights the central sulcus of the brain had narrowed. This was seen in 3 of 16 short duration astronauts. Following all long duration missions there was an upward shift of the brain and narrowing of cerebrospinal



production of CNS myelinating cells. Participants were patients (n=50) who have been diagnosed with relapsing MS for less than 15 years. The primary outcome was assessing change in visual nerve transmission. By the end of the study, clemastine fumarate treatment had significantly reduced latency delay nerve transmission in eyes. No serious adverse events were reported but treatment was associated with fatigue. This is the first controlled study to demonstrate myelin repair in those with chronic demyelinating MS, even after prolonged damage.

Green AJ, Gelfand JM, Cree BA, et al. Clemastine fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomised, controlled, double-blind, crossover trial. *Lancet* 2017; 390: 2481–2489.

### Nerve grafting for spastic limb paralysis

Spastic limb paralysis caused by stroke, brain injury or a cerebral palsy is a long-term disability. Spastic posture can provoke major impairment to activities of daily living such as hygiene and dressing, as well as causing pain. A study has investigated if grafting of the contralateral C7 nerve (from the unaffected side) can restore some function in patients. Patients with unilateral arm paralysis (n=36) present for more than 5 years were randomised (1:1) to either undergo C7 nerve transfer plus rehabilitation, or rehabilitation alone. Any improvement was measured using a scoring scale and primary outcome was improvement on this scale from baseline at 12 months. The surgical grafting cohort had a significantly higher mean improvement than the rehabilitation alone group ( $p < 0.001$ ) and imaging techniques supported success of nerve connectivity. There was no reduction in power, tactile threshold or sensation in the hand of the donor side. Grafting of C7 resulted in a reduction in spasticity and improvement in function when combined with rehabilitation versus rehabilitation alone.

Zheng MX, Hua XY, Feng JT, et al. Trial of contralateral Seventh Cervical Nerve Transfer for Spastic Arm Paralysis. *NEJM* 2018. 378:22–34

## Paediatrics

### Neuroprotection for preterm infants

Preterm birth increases the risk of both death within the first week of life and cerebral palsy. Effective therapies to re-

duce the risk of adverse neonatal neurological outcomes are well needed. Magnesium sulphate may reduce the risk of such adverse outcomes when given to pregnant women at risk of preterm birth. Researchers have compiled data from five randomised trials including data on over 6,100 preterm (<37 weeks' gestation) infants whose at-risk mothers were given magnesium sulphate or control treatment prior to preterm birth. Antenatal magnesium sulphate given to women at risk of preterm birth was found to reduce the risk of infant death or cerebral palsy in infants born preterm. These benefits were seen regardless of the reason for risk of preterm birth. This highlights a potential strategy for combating the burden of death and cerebral palsy in babies born prematurely that is both inexpensive and effective.

Crowther CA, Middleton PF, Voysey M, et al. Assessing the neuroprotective benefits for babies of antenatal magnesium sulphate: An individual participant data meta-analysis. *PLoS Med* 2017; 14(10): e1002398. <https://doi.org/10.1371/journal.pmed.1002398>

### First trimester weight gain associated with birth weight

Gestational weight gain partly determines infant birth weight but we do not know if the chronology of maternal weight gain during pregnancy is important and previous studies have provided conflicting data on this. A preconception cohort study in China has set out to evaluate the influence of pregravid weight and weight gain throughout pregnancy on infant birth weight. The study included over one thousand newly married women who underwent weight measurements starting at an average of 19 weeks prior to pregnancy followed by measurements at 10 gestational intervals. Pregravid weight was found to be strongly associated with infant birth weight. However, among the 10 gestational intervals, only the weight gain up to 18 weeks was associated with infant birth weight. For pregravid to 14 weeks, birthweight was associated with 14 g per kilogram of maternal weight gain and for 14–18 weeks the association was 26 g per kilogram of maternal weight gain. Understanding that early weight gain is influential in infant birth weight may help provide a critical window for interventions to help influence infant birth weight.

Retnakaran R, Wen SW, Tan H et al. Association of Timing of Weight Gain in Pregnancy With Infant Birth Weight. *JAMA Pediatr*.

### Long-term consequences of childhood kidney disease

Early intervention for those at risk may help reduce the global burden of chronic kidney disease and end-stage renal disease (ESRD). Childhood kidney disease can progress to a chronic disease whilst still in childhood and we know that this group can go on to develop ESRD. However, there is a population of children with kidney disease who go into adolescence disease-free. Data on the long-term renal health of this healthy adolescent population has previously been unclear. A historical cohort study of Israeli adolescents included data taken from between 1967 to 1997. Childhood kidney disease included congenital abnormalities, pyelonephritis and glomerular disease. At adolescence, all children included in the study had normal renal function and no hypertension. Adults with normal renal function in teenage years on a background of childhood kidney disease had a significantly increased risk of ESRD, suggesting long term implication of childhood renal disease. This highlights a group who could benefit from early identification and intervention.

Calderon-Margalit R, Golan E, Twig G, et al. History of Childhood Kidney Disease and Risk of Adult End-Stage Renal Disease. *NEJM* 2018; 378:428–438 DOI: 10.1056/NEJMoa1700993

## Miscellaneous

### Health benefits of coffee

Coffee is one of the most widely consumed beverages worldwide. As such, it makes sense that we understand what, if any, health impacts its consumption has. A review has looked at over 200 meta-analyses of observational research and 17 analyses of interventional research where health outcomes associated with coffee consumption were interpreted. It was found that coffee consumption was more often linked with benefit to consumers than harm. For several outcomes, including overall cause mortality and cardiovascular mortality, consumption of three to four cups of coffee a day versus none was associated with a greater reduction in risk. High coffee consumption was associated with an 18% lower risk of incident cancer than with low coffee

consumption. Coffee drinkers were also found to benefit from a lower risk of several specific cancers, neurological, metabolic and liver conditions. However, high coffee consumption was found to be associated with adverse birth outcomes including preterm birth in pregnant women. Coffee drinking was also associated with risk of fracture in women.

Poole R, Kennedy OJ, Roderick P, et al. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. *BMJ* 2017; 359 :j5024

### Ultra-processed foods and cancer risk

Lifestyle habits have a major influence over the development of cancers. A study has looked at the impact of processed food intake on risk of overall, breast, prostate and colorectal cancers. Food items were categorised according to their degree of processing by the NOVA classification. Ultra-processed foods may contain high levels of fat, sugar and salt with a lower density of nutrients. They may also contain controversial additives and be contained in packaging that contains carcinogenic material. The study found that ultra-processed food intake was associated with an overall higher risk of cancer. Several surveys have found that this group of foods may contribute to between 25% and 50% of total daily energy intake. Even a 10% increase in the proportion of ultra-processed foods in an individual's diet was associated with an increased risk of greater than 10% for overall and breast cancers. These are modifiable risk factors and by identifying them and reducing our involvement with them we can reduce our risk of several cancers.

Fiolet T, Srour B, Sellem L, al. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. *BMJ* 2018; 360 :k322

### Oral capsule delivered faecal microbiota

*Clostridium difficile* infection (CDI) is the major cause of hospital acquired infectious diarrhoea. Recurrent CDI (RCDI) has been shown to be effectively reduced with faecal microbiota transplantation (FMT) with an efficacy of between 60-90% following a single treatment. Previous studies have already shown that frozen-and-thawed FMT is non-inferior to fresh FMT against RCDI. A team in the Canada have investigated if the route of delivery has any consequence

on efficacy in a non-inferiority trial. Participants were randomly assigned to receive FMT either by oral capsule or by colonoscopy. A follow up at 12 weeks post the single-dose treatment revealed that 96% of participants in each group were recurrence free. Participants significantly preferred the oral capsule delivery and the risk of minor adverse events was lower at 5% with capsule versus 12% with colonoscopy. Faecal microbiota transplantation delivered by oral capsule is non-inferior to colonoscopy and may be an attractive alternative to colonoscopy delivered methods in the treatment of recurrent *Clostridium difficile* infection.

Kao D, Roach B, Silva M, Effect of Oral Capsule—vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent *Clostridium difficile* Infection: A Randomized Clinical Trial. *JAMA*. 2017;318(20):1985–1993. doi:10.1001/jama.2017.17077

### Cardiopulmonary responses to walking in pollution

Air pollution is a major environmental health risk. We know that long term exposure to pollutants can decrease lung function in older individuals and those with chronic obstructive pulmonary disorder (COPD). In addition, shorter term exposure to pollution has been associated with increased mortality in ischaemic heart disease (IHD) and COPD. Walking has been shown to result in beneficial cardiorespiratory effects. A study has compared outcomes of healthy volunteers and volunteers with COPD or ischaemic heart disease aged 60 and older walking on either heavily polluted streets or urban green space. The aim was to assess the effects on respiratory and cardiovascular responses to walking down a busy street that is high in pollution versus a traffic free area. In all participant groups walking in the green low-pollution environment led to an increase in lung function. These positive responses were negated by walking in the high pollution area. Short-term exposure to traffic pollution prevents the beneficial cardiopulmonary effects of walking in people with COPD, IHD and those free from cardiopulmonary disease.

Sinharay R, Gong J, Barratt B et al. Respiratory and cardiovascular responses to walking down a traffic-polluted road compared with walking in a traffic-free area in participants aged 60 years and older with chronic lung or heart disease and age-matched healthy controls: a randomised, crossover study. *The Lancet* 2018; 391:339 - 349



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## Questions

Test your knowledge against the Clinical Review articles from pages 29 to 33.

### Clinical Review: Paediatrics

Identify which is the correct statement

1. In early neonatal sepsis Group B streptococcus...
  - (a) Is more common in low- and middle-income countries
  - (b) Can be prevented by intrapartum antimicrobial prophylaxis
  - (c) Is treated with gentamicin
2. Early neonatal sepsis is associated with...
  - (a) Low maternal vitamin D levels
  - (b) Candida infection
  - (c) Mechanical ventilation
3. C-reactive protein...
  - (a) Is produced by the bone marrow
  - (b) Should have serial measurements
  - (c) Is higher in very low birth weight infants

### Clinical Review: STIs

5. Name two advantages and two disadvantages of syndromic management of STIs.

6. Complete this statement by choosing from the answers below. Point of care (POC) testing for STIs...

- (a) Is crucial for confirmation of specific infection
- (b) Is rapidly evolving
- (c) Facilitates diagnosis and treatment in one visit
- (d) Can be expensive

7. Name two re-emerging or newly recognised STIs

### Clinical Review: Pharmacy

8. Under European law, does a falsified medicine contain the correct quantity of the active ingredient but with a fake label?
9. Which of these are safe to treat cardiovascular disease in pregnancy?
  - (a) Low dose aspirin
  - (b) Verapamil
  - (c) Hydrochlorothiazide
10. What are the drugs with the highest risks of serious adverse drug reactions?

### CPD Answers

1. B of syndromic management of STIs are: asymptomatic infections are not detected, overtreatment of those not infected, no confirmation of specific infection, and no detection of antimicrobial resistance
2. A are: low-cost, simple to follow, does not require laboratory testing, allows for treating mixed infections, enables diagnosis and treatment in one visit. Some of the disadvantages
3. B
4. detail awaited
- 5: A few of the advantages of syndromic management of STIs are: low-cost, simple to follow, does not require laboratory testing, allows for treating mixed infections, enables diagnosis and treatment in one visit. Some of the disadvantages
- 6: All of the descriptions are correct
- 7: Shigellosis, a diarrhoeal disease, caused by the bacterium shigella,
8. No. A falsified medicine does not contain the correct quantity of the active ingredient.
9. All of them
10. NSAIDs, anticoagulants (e.g., warfarin), antiplatelet drugs (e.g., aspirin)



# Migraines and pregnancy (answers on page 34)

## Part one

Mary is 23 and is in the early stages of her first pregnancy. A university graduate in maths, she is bright and intelligent, but burdened with migraine, from which she has suffered since early childhood. She is worried that her migraine will worsen during her pregnancy – she is already experiencing more headaches than usual – and also whether her migraine treatment and prophylaxis may harm her developing baby.

- Q1 What are your top three priorities for Thomas?**
- (a) Migraines usually lessen during pregnancy so she can be reassured.
  - (b) The above only applies to premenstrual migraine and migraine without aura.
  - (c) Are the headaches Mary describes really part of her usual migraine attacks?
  - (d) How does her migraine usually present?
  - (e) If she is reasonably well controlled on her usual treatment, it isn't necessary to change it, as the risk of making her migraine much worse during this crucial period is too high.

## Part two

- Q2 Which of the following non-pharmaceutical treatments have been shown to help reduce migraine attacks and severity?**
- (a) Hydrate with 2 litres of water per day.
  - (b) Don't skip meals.
  - (c) Get 7 to 8 hours of sleep at night.
  - (d) Avoid bright lights (even mobile phone use) at night.
  - (e) Regular exercise.
  - (f) Stop all caffeine containing drinks.

## Part three

Mary is using ibuprofen to treat her migraine attacks along with cyclizine to deal with the nausea that often accompanies the headaches. She is also taking aspirin 75mg daily as prophylaxis. If these don't work well, in the past her doctor has added once daily propranolol and occasionally low dose amitriptyline at night.

- Q3 What is your opinion about continuing this regimen during pregnancy?**
- (a) She should avoid opiates as they worsen pregnancy nausea.
  - (b) Low dose aspirin has been shown to help prevent migraine during pregnancy and is safe up to the 36th week.
  - (c) Ibuprofen should not be used in the third trimester as it may cause premature closure of the ductus arteriosus.
  - (d) Betablockers such as propranolol may cause foetal anomalies if given in the first 12 weeks.
  - (e) Amitriptyline has not been shown to be safe during pregnancy.
  - (f) Antiemetics such as cyclizine, prochlorperazine, ondansetron and domperidone may affect the foetus and should be prescribed only if vomiting becomes severe.
  - (g) Long term, metoclopramide may lead to extrapyramidal symptoms.

## Part four

- Q4 Women with migraine in pregnancy have been shown to be at higher than normal risk of several complications. Which of the following should you (and she) be aware of?**
- (a) Pre-eclampsia.
  - (b) Gestational hypertension.
  - (c) Arterial thrombosis.
  - (d) Venous thrombosis.
  - (e) Glaucoma.
  - (f) Orthostatic headache.

Quiz by Dr Tom Smith



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