Africa HEALTH

September 2014 Volume 36 Number 6

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Can Ebola deliver a legacy?

No apologies, but this issue is Ebola heavy. The extraordinary outbreak in West Africa, the worst in the four decades since the disease was first recorded, caught everyone unawares. In reality, given the foothold it established after going unrecognised for several months within an extremely rural and poor region, it is remarkable that only one case was carried (to Nigeria) beyond the immediate epicenter of Liberia, Guinea and Sierra Leone.

I am in Lagos as I write, where tragically one traveller from Liberia has taken out five health professionals with several more in isolation. A similar number of naïve residents have perished from what can only be described as 'paranoia and fear' having resorted to ill-advised 'prophylaxis' against the disease such as salt baths.

We can only imagine what it is like in the hub area of Sierra Leone, Liberia and Guinea, in which perhaps as many as a million people have been sealed in and quarantined from the rest of the world. Eyewitnesses from Médecins Sans Frontières used the words 'war zone' to describe what they saw.

If you know about Ebola, you will know that it is actually very difficult to catch. In crude terms: avoid fruit-bat pie, and don't touch acutely ill or dead people. For the public that should be reassuring, though the media hype against a scary haemorrhagic disease has occluded the message. But for health professionals of course the challenge is much more acute, especially bearing in mind the shortage of quality protective clothing. In all areas the Ebola crisis has really focused minds on the enormously difficult role that frontline health professionals are expected to undertake in Africa, very often without even the most basic of resources. Many have died. Many have fled.

A myriad of issues have been raised, and maybe, just maybe, the wake up from this will provide a positive legacy. This outbreak will die back, though it may take some months, but that won't mean it has gone away. Ebola is not like Haley's comet, it might go away now, but for sure it will be back maybe in the same place, maybe somewhere else. Or it could be a resurgence of Lassa or Marburg, or an entirely new virus, all equally scary.

The diseases are not new so it was also interesting to observe the debates over whether it was ethical to use 'untested' (non FDA'd) potential cures. I recall visiting Kenema in North Eastern Sierra Leone back in the 1980s and meeting a team from a USA military-led Lassa fever research team. They explained that over 70% of the local population were carrying antibodies to Lassa, so clearly it was endemic, though maybe not at its most virulent level seen in some outbreaks. One suspects ZMapp, the 'untested' treatment which seemed to work for the two US health workers who are now discharged from hospital was an outcome of research such as this. But it does make you wonder why, thirty years on, no one has been able to move this research into tried and tested products on the ground, rather than a tiny number of treatments for a few selected cases.

Bryan Pearson
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Cure for Ebola virus disease

The fast-tracking of ZMapp for human use in the current Ebola outbreak is notable. Professor Shima Gyoh looks into the background of this intriguing development

It is becoming clearer to me that I do not belong to this era. The landing on the moon was too remote from me to properly wonder, but many miracles do involve me, personally. I flew from Paris to San Francisco in what seemed to me like a flying village. Yes, much more than a flying house, for I know of many villages in my local government with no more than five families, but I have never heard of a house in which 500 people lived. That was the content of the Airbus 380 that took me to San Francisco, and I sat upstairs! It is bad enough for me to sit in a craft carrying 20 people and still be able to take off, but this huge beautiful monster, weighing 560 tons that can reach its cruising height of 39000 feet in less than 15 minutes, simply leaves me breathless with wonder.

In the medical field, development of the drug against Ebola virus astounds me. ZMapp, the antiserum for Ebola that has been catapulted to fame too early in its scientific history has a most intriguing origin. The sting of the Ebola virus is a glycoprotein that enables it to attach itself to human cells. The company Mapps set out to find a way of neutralising this glycoprotein.

First, mice were infected with Ebola virus. The antibodies they produced against the glycoprotein were extracted, tested and found to be active. Then the cell responsible for its production in the mouse was isolated and fused with a cancer cell to enable it to replicate rapidly and produce the antibodies.

However, the resultant antiserum was mouse protein and would stimulate severe rejection in the human; so it needed to be humanised. Sections of its molecules were spliced and replaced with human protein, care being taken to avoid removing the parts that were relevant to neutralising the Ebola glycoprotein.

The next stage was to produce the now humanised antibody in large quantities, so the gene was then injected into the genome of Nicotiana, a tobacco plant. This was done through two plant viruses via the Agrobacterium (known for its ability to transfer DNA between itself and plants) as an intermediate step. The plant now produced the antiserum which was harvested and purified, QED!

John Trimmer who explained the process said[1] 'If the process described above - with infinite antibodies, cloning, mixing genes from different species, and mass production in plant cells - sounds like science fiction, it shouldn't. Every single one of those procedures is well established and has probably been used by a hundred biotech startups by now. Biotech doesn't tend to get the same attention as the work done by the people who make our processors and batteries, but it's some of the most amazing technology on the planet.'

I totally agree.

Trial in monkeys has shown that the drug is effective even for prophylaxis, but it had not yet to undergone human trials when two American health workers lay dying of Ebola in Liberia. They were given it as a desperate measure when the symptoms that precede death were noticed. Dr. Kent Brantly developed dyspnoea and Mrs Nancy Writebol was extremely prostrate and weak. The situation was hopeless, and, as Mrs Writelbol's husband said on CNN, the family was preparing for her funeral. Administration of ZMapp was a desperate last minute risk.

Fortunately, Dr. Brantly showed dramatic improvement, but scientifically, it would be reckless to jump to the conclusion that the drug did it. Science insists we must not regard 'post hoc, propter hoc' as deduction that is always true. Brantly had previously had a blood transfusion from a 24-year old boy that survived Ebola. The dramatic improvement might have already been in the works and drug injection an entirely fortuitous coincidence. ZMapp would have to produce consistently positive results in many different patients before the medical world would accept it as truly efficacious.

Its effect on the lady has been, well, good but less dramatic, justifying treading with caution. On the other hand, the Spanish priest who died despite the injection does not necessarily invalidate its claim to efficacy. Still, the question of tolerance, the correct dose, and the timing of administration are all crucial requirements usually determined at clinical trials and serve to guide doctors using the drug.

Suppose the drug was first tried on Africans? I can best quote[2] the Director of Caprisa, an AIDS research centre in South Africa:

'It would have been on the front page with screaming headline: Africans used as guinea pigs for American drug company's medicine.' Heads I loose, tails you win!

The World Health Organization approval for use of ZMapp would also serve for clinical trials, but it amounts to putting the cart before the horse as approval at this level is usually done only after clinical trials.

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

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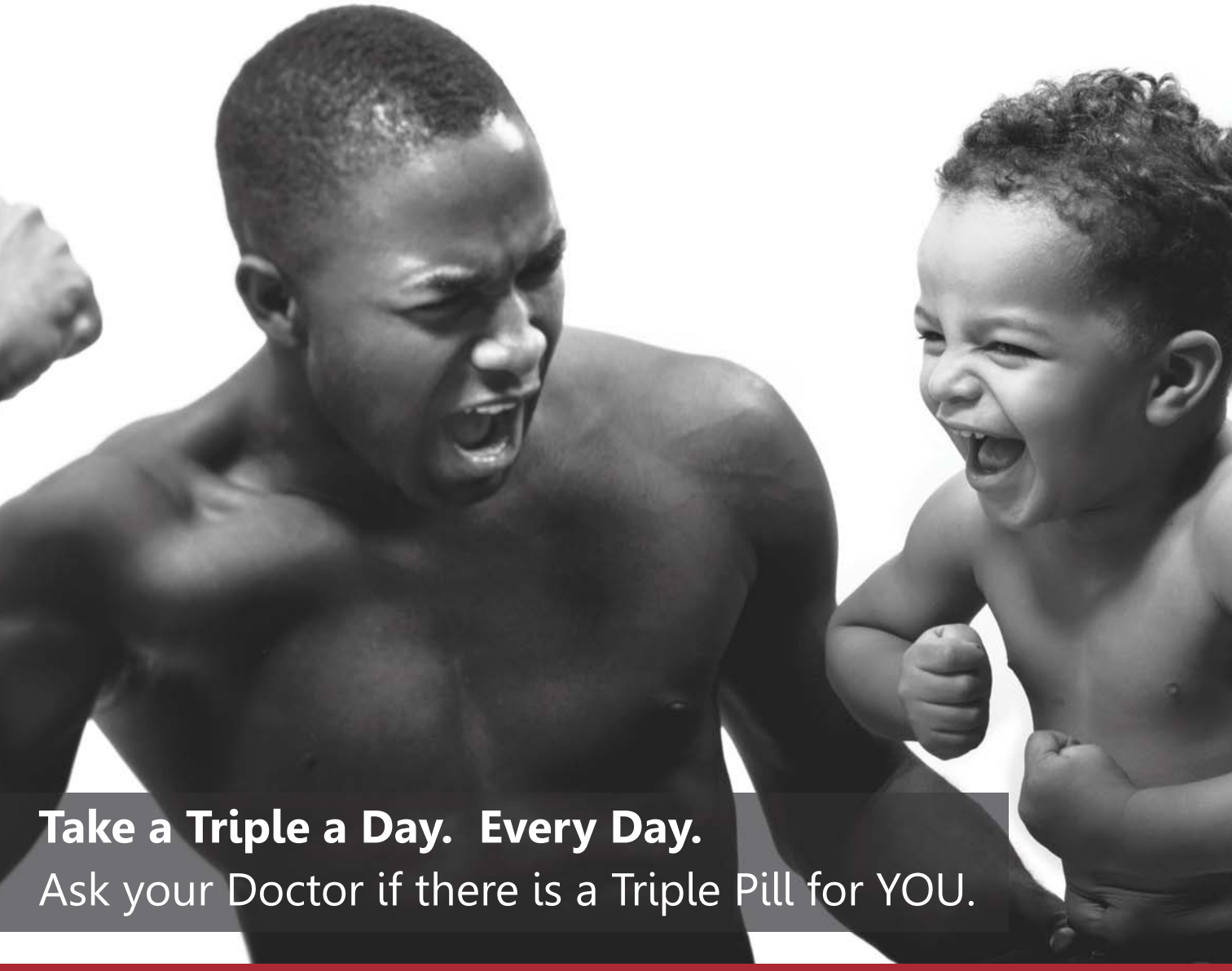

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Let us all prepare for Ebola

Valuable lessons were learned during the Ebola outbreak in Uganda in 2000. Trying to ensure a legacy to take forward is equally important. Francis Omaswa was in the hot-seat in 2000

The Ebola Hemorrhagic fever outbreak afflicting a number of West African countries has become a real African and global threat. Travelling via Nairobi or Addis Ababa, the two major airline hubs that connect west and east Africa, we are warned to be careful and to avoid contact with crowds, or to cancel air travel all together. Many health workers have succumbed to the infection in the affected countries and the USA is evacuating their infected health professionals using very high cost air ambulances. There is panic among communities in the affected countries. The governments and the international agencies have weighed in. However, it appears that a trust gap has developed between the health system and the general population which has made control efforts difficult in West African countries. So, how can this trust be regained?

Until the current West African Ebola outbreak, Uganda held the record for the largest epidemic with 425 recorded cases of Ebola during the year 2000. I was then Director General of Health Service's and oversaw efforts to control this epidemic. What lessons did we learn in Uganda?

The single most important lesson is that building and holding public trust by the government and health personnel is the foundation for all control efforts. Ebola evokes fear and apprehension at individual and community level which easily results in herd responses; negative or positive. We achieved public trust in Uganda through very intensive communication with the public. Epidemic status reports were issued through press statements every morning, lunchtime, and evening, along with a press conference each morning. The media are critical in building and sustaining trust and their own confidence has to be won. This was not easy and required personal sessions with the leaders of the media houses on a regular basis. There were also hotlines for anyone to seek or convey information, which was open 24 hours at the Ministry of Health Headquarters and at the District Medical office in the affected districts.

The second key intervention we made was the recruitment of the support of community or village leaders working alongside the Village Health Teams who are a cadre of community health workers that already existed in the public health system structures. Controlling the epidemic is about early detection, isolation, treatment of new infections, contact tracing, including safe handling of body fluids, and the remains of those who die. This can only happen by staying very close to all families and households, and this was achieved by building community trust of the public health system, including recruiting the support and oversight by local formal and informal community leaders. Top Ministry officials moved to live in the effected districts to support and direct control efforts, and the Minister and Director General visited weekly using helicopters to go to the villages, addressing public meetings and inspiring local health workers.

The third key intervention was the introduction of Technology for quick field diagnosis of new infections. This enabled suspected, but negative individuals, to leave isolation quickly and return to normal life. It also enabled early initiation of treatment measures for those who test positive. This was the contribution of partners such as the Centers for Disease Control from the USA, who brought in a field laboratory and World Health Organization that came with supplies and technical expertise to support and stay with us in Uganda. This global solidarity however, can only work where there is effective local leadership that is trusted by the local population.

Finally, controlling an Ebola outbreak is about strong primary healthcare strategies that we have always aspired for; namely leadership from the top, integrated with routine governance of society and involving the active participation of the people themselves. Once we have controlled this outbreak, let's institutionalise these practices because we need them anyway, but also because there will be another Ebola outbreak soon enough.

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

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Ebola to run into 2015; fears for patients with other diseases

As Africa Health went to press, the official death-toll from Ebola was close to 1500 and the international agencies involved in the fight to control its spread, were laying plans which stretched well into 2015. Dr. David Nabarro, Senior United Nations System Coordinator for Ebola who was appointed by the Secretary-General to establish how best the UN can support affected communities, was wrapping up the first leg of a visit to all Ebola-effected countries in West Africa.

In the Liberian capital, Monrovia, he identified the need to somehow bring in more healthworkers to the country to deal with the outbreak, saying: 'The United Nations is looking at ways to radically scale up support to fight Ebola.' Dr. Keiji Fukuda, UN World Health Organization (WHO) Assistant Director-General for Health Security, provided reassurance 'This is not a hopeless situation.'

But as if to reinforce how difficult it is to deal with the multi-dimension cultural issues, WHO was exclaiming its surprise at how as fast as they opened up isolation centres, so they were being filled. The sense was that many people with the disease were being kept out of sight by their families. The invisible caseload was leading to a rapid reappraisal of actual numbers of cases. The health agency went on to say that in rural villages, corpses are buried without notifying health officials and with no investigation of the cause of death. In some areas, most notably Monrovia, virtually all health services have shut down.

Meanwhile, there is rising concern that because of Ebola many more people will die of malaria, pneumonia, diarrhoea and other diseases, simply because they may be suspected of having Ebola and find it difficult to get care. An article in *Bloomberg Businessweek* used the global burden of disease estimates to put the numbers of deaths in perspective: for example, 298 people died from Ebola in approximately four months in Sierra Leone compared with an estimated 650 from meningitis, 670 from tuberculosis, 790 from HIV/AIDS, 845 from diarrhoeal diseases and more than 3000 from malaria.

Ebola research: rapid funding initiative

An emergency call for research projects on Ebola that will tap into a humanitarian crisis fund has been launched by UK-based medical research charity the Wellcome Trust and the UK's Department for International Development.

The call aims to better inform the fight against current and future Ebola outbreaks, and is open to researchers worldwide in fields including anthropology, clinical management, diagnosis, disease control and prevention, ethics, health systems, social mobilisation, surveillance and treatment.

'What we learn could also change the way we approach future outbreaks, providing us with tested tools and techniques that were not available to public health authorities this time,' said Jeremy Farrar, of the Wellcome Trust.

The deadline is 8 September and the idea is to immediately review proposals to allow researchers to start work as soon as possible.

SciDev news says it is unclear how much money will be made available from the US$10.8 million within the overall Research for Health in Humanitarian Crises (R2HC) fund.

A Wellcome Trust-DFID press release says: 'The size and number of grants to be awarded will depend on the number of high-quality applications received that are within the scope of the call.'

In the release, Justine Greening, the UK's international development secretary, added: 'This will help us better equip those working on the ground so they can tackle the outbreak as effectively as possible and prevent more people contracting this terrible disease.'

Wellcome Trust director Jeremy Farrar said in the release: 'We believe rapid research into humanitarian interventions and therapeutics can have an impact on treatment and containment during the present outbreak.'

Malawi Adventist Health Services gets $2.5m USAID grant

The United States International Development (USAID) has granted $2.5 million to Malawi Adventist Health Services (AHS) to train healthcare workers and expand provision of family planning services for the period of three years, from June 2014 to June 2017.

The project is targeting 400 000 people with 272 271 women and 163 909 men in four districts of Dedza, Rumphi, Mzimba and Blantyre.

According to a statement from the agency, reaching out with contraceptives choice in Malawi, the project will provide voluntary, comprehensive family planning services to women and men of reproductive age in rural areas of the mentioned districts.

A statement from the agency says: 'The agency's family planning reproductive health activities strengthen the health system to deliver quality family planning services equitably, efficiently, and in a coordinated manner. Family planning is essential for Malawi's sustainable future.'

During the implementation period, it said, AHS will partner with the Ministry of Health, Women and Children First (WCF), a UK-based organisation that has pioneered a community mobilisation approach which empowers communities through a Participatory Learning and Action Cycle.

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Ethical considerations for use of unregistered interventions for Ebola viral disease

The Ebola virus outbreak in West Africa is well documented in this issue. The following report is from World Health Organization (WHO) following its convening of a high level consultation on the use of unregistered medicines.

Ebola outbreaks can be contained using available interventions like early detection and isolation, contact tracing and monitoring, and adherence to rigorous procedures of infection control. However, a specific treatment or vaccine would be a potent asset to counter the virus.

Over the past decade, research efforts have been invested into developing drugs and vaccines for Ebola virus disease. Some of these have shown promising results in the laboratory, but they have not yet been evaluated for safety and efficacy in human beings. The large number of people affected by the 2014 West Africa outbreak, and the high case-fatality rate, have prompted calls to use investigational medical interventions to try to save the lives of patients and to curb the epidemic.

Therefore, on 11 August 2014, the WHO convened a consultation to consider and assess the ethical implications for clinical decision-making of the potential use of unregistered interventions.

In the particular circumstances of this outbreak, and provided certain conditions are met, the panel reached consensus that it is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects, as potential treatment or prevention.

Ethical criteria must guide the provision of such interventions. These include transparency about all aspects of care, informed consent, freedom of choice, confidentiality, respect for the person, preservation of dignity, and involvement of the community.

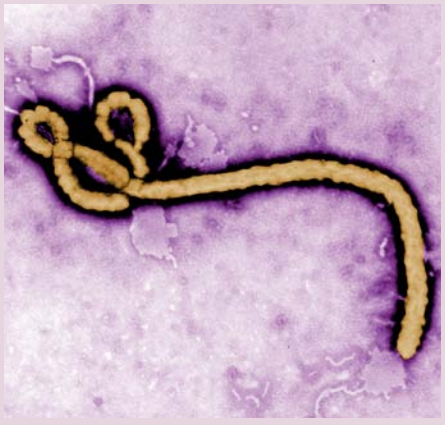
In order to understand the safety and efficacy of these interventions, the group advised that, if and when they are used to treat patients, there is a moral obligation to collect and share all data generated, including from treatments provided for 'compassionate use' (access to an unapproved drug outside of a clinical trial).

The group explored how the use of these interventions can be evaluated scientifically to ensure timely and accurate information about the safety and efficacy of these investigational interventions. There was unanimous agreement that there is a moral duty to also evaluate these interventions (for treatment or prevention) in the best possible clinical trials under the circumstances in order to definitively prove their safety and efficacy, or provide evidence to stop their utilisation. Ongoing evaluation should guide future interventions.

In addition to this advice, the panel identified areas that need more detailed analysis and discussion, such as:

- ethical ways to gather data while striving to provide optimal care under the prevailing circumstances;
- ethical criteria to prioritise the use of unregistered experimental therapies and vaccines;
- ethical criteria for achieving fair distribution in communities and among countries, in the face of a growing number of possible new interventions, none of which is likely to meet demand in the short term.

Photo credit (below): Reuters Ministry of Defence Handout - via Reuters



Bush rallies support for women's health issues in Africa

Former President George W. Bush made a rare Washington appearance, urging the spouses of African leaders at a day-long symposium to do more to reduce the 'stigma and ignorance' that he said still surrounds diseases that strike women.

Bush noted that many women aren't getting treated because of the stigma, and 'some false rumors.'

While those barriers 'may seem like an unbreakable wall,' he said, 'it's really made of glass and through your leadership it can be broken.'

Bush took the stage following a discussion led by his wife, former first lady Laura Bush, and first lady Michelle Obama, to highlight the ways political spouses can make a difference, with an emphasis on improving the lives of women and girls across Africa.

The symposium was part of the US - Africa Leaders Summit,designed to bolster economic ties between America and Africa.

'You all have the potential to inspire millions across the globe,' Obama said. 'It is my hope that today, we will rededicate ourselves to these efforts and commit to new efforts to lift up our young people.'

The former president said that his 2003 President's Emergency Plan for AIDS Relief, known as PEPFAR, was launched to stem a pandemic. Thanks to two US administrations and increasing commitment from African countries, it now serves to stave off AIDS in more than 9 million people in sub-Saharan Africa.

'Disease can be defeated, and people living with AIDS refuse to be defeated,' he said. 'A generation on the verge of being lost has been found.'

But Bush noted there's still a stigma attached to AIDS and HIV infection, and that women and girls are particularly vulnerable. Women with HIV, he noted, are more likely to develop cervical cancer, a preventable but leading cause of death.

He announced that a Bush initiative, Pink Ribbon Red Ribbon, which aims to include cervical cancer prevention in sub-Saharan Africa and Latin America, including increased access to human papillomavirus vaccinations in routine healthcare, will be expanded to Namibia and Ethiopia.

He noted African first ladies have been fighting against the 'false rumors of the HPV vaccine.'

The two first ladies shared the stage, talking warmly about serving as modern first ladies and championing efforts to empower women.

Giant rats trained to sniff out tuberculosis

The Eduardo Mondlane University College of Veterinary Medicine in Mozambique has trained giant African pouched rats to sniff out tuberculosis (TB).

Training rats to detect TB is a relatively new endeavor for APOPO, the Belgian non-profit organisation that's best known for using rats to find land mines. APOPO began using TB rats in Tanzania in 2008, and in Mozambique in 2013. Currently, the animals work in 21 medical centres in Dar es Salaam, and double-check 75% of potential TB samples from medical centres in Maputo.

Like the battle against land mines, the fight against TB, which claimed 480 000 lives in Africa in 2012, 58 000 of them in Mozambique, according to the World Health Organization, is badly in need of an innovative, rapid, and affordable detection technique.

'We know that we need a new approach in the diagnosis of TB, so this could be one of the approaches,' said Gaël Claquin, a TB/HIV specialist in Mozambique.

In the first 16 months of the Maputo programme, the rats evaluated samples from roughly 12 500 patients. Of those, 1700 had been found positive at the health clinics. The rats detected another 764 patients, an increase in detection rate of around 44%, according to APOPO.

After undergoing nine months of training in Tanzania, the rats are put to work.

'What the rats are trained to do is associate the smell of TB with a reward, so it's what they call operative conditioning,' Emilio Valverde, manager of the APOPO Mozambique TB Programme said.

It is the same principle applied to detecting land mines, only the rats are trained to recognise the scent of specific molecules that reflect the presence of the TB germ.

To keep the animals motivated, positive samples are mixed in with the unknown samples. When the rat alerts by scratching at a known sample, a buzzer is sounded and the rat is rewarded with a treat.

Any suspect samples are triple-checked, and if found to be positive, they're reported back to the clinics.

Each rat costs around $6700 to $8000 to train, but relatively little to maintain over their six-to-eight-year life span, said Valverde.

Emilio Valverde is excited about its potential and curious to know whether male and female rats perform differently, whether they might be able to detect latent TB, or identify TB about to become active.

Artemisinin resistance holding-up in Africa

A long-term study at three sites in Africa indicates that while drug-resistant malaria has proved to be a serious threat in many parts of Asia, there are no signs yet of it showing up in Africa.

'It may still be possible to prevent the spread of artemisinin-resistant malaria parasites across Asia and then to Africa by eliminating them, but that window of opportunity is closing fast,' Nicholas White, a professor of tropical medicine at Oxford University says. White has led current research and is chair of the Worldwide Antimalarial Resistance Network. Analysing blood samples from 1241 malaria patients in 10 countries across Asia and Africa, researchers found resistance to the world's most effective antimalarial drug, artemisinin. While drug-resistant malaria is now widespread in Southeast Asia, there are signs that it has yet to gain a foothold in Africa.

Malaria remains a very worrisome condition for the majority of the world's population. More than half the world's people are at risk of malaria. Those most at risk are children younger than five years old living in the poorest parts of sub-Saharan Africa. The problem certainly has historical precedence. From the late 1950s to the 1970s, chloroquine-resistant malaria parasites spread across Asia to Africa, leading to a resurgence of malaria cases and millions of deaths. Chloroquine was replaced by sulphadoxine-pyrimethamine. Resistance again was developed and malaria re-emerged in western Cambodia and spread to Africa. Artemisinin combination treatment (ACT), currently in the frontline for malaria treatment, may now fall by the wayside in efforts to combat the disease.

The latest study enrolled infected adults and children at 15 trial sites in 10 malaria-endemic countries between May 2011 and April 2013. Patients received a six-day antimalarial treatment, three days of an artemisinin derivative, and a three-day course of ACT. Researchers analysed their blood to measure the rate at which parasites are cleared from it and from those measurements were able to deduce resistance levels.

Quarter of world population to be Africans by 2050

Africans will count for a quarter of the world population in 35 years from now, a United Nations agency report has revealed.

The United Nations Children's Fund (UNICEF) demographics report states that Africa will be home to two out of five children in the world by 2050, which will translate to 25 out of 100 people living in the world being Africans.

The global population projections indicate that by mid-century, Africa will be home to around 41% of all the world's births, 40% of all global under-fives, 37% of all children under-18, and 35% of all adolescents.

The UNICEF report dubbed Generation 2030/Africa Report states that the future of humanity is increasingly African as today, 16 among 100 of the world's inhabitants are African, and based on current trends, within 35 years, 25 in 100 people will be African, with this likely to continue to rise to almost 40 in 100 people by the end of the century.

Worldwide, Africa is the only region where the population is projected to keep increasing throughout the 21st century. Currently, there are 1.2 billion people in Africa, more than five times the population in 1950. By 2050, Africa's population will double, to 2.4 billion and eventually reaching 4.2 billion by the end of the century.

'This is an unprecedented projected increase in Africa's child population size provides policymakers with a once-in-a-generation opportunity to craft a child-focused investment strategy that enables the continent, and the world, to reap the benefits of Africa's demographic transition,' UNICEF said in the report.

According to the Generation 2030/Africa Report, high fertility rates and rising numbers of women of reproductive age mean that over the next 35 years, almost two billion babies will be born in Africa; the continent's population will double in size; and its under-18 population will increase by two-thirds to reach almost a billion children.

Among the report's most important findings is a massive shift in the world's child population towards Africa. Projections indicate that by 2050, around 40% of all births, and about 40% of all children, will be in Africa, up from about 10% in 1950.

Applications are in for 2014's Healthcare Innovation Award

Applications are now in for the 2014 $1 million Healthcare Innovation Award, as previous winners attract interest and support from national governments to help improve survival rates of newborns and children under five in developing countries.

Six months after receiving a share of the 2013 Healthcare Innovation Award, five organisations based in developing countries are helping shape national health agendas and influencing approaches to healthcare for children and newborns.

The top-prize winner from 2013 was a low-cost Continuous Positive Airway Pressure (CPAP) kit, developed by Friends of Sick Children (FOSC) in Malawi. This device helps premature and newborn babies suffering from distress breathe more easily. With funding from the Award, and backing from the Ministry of Health in Malawi, FOSC is now sharing this technology with teaching hospitals in Tanzania, Zambia and South Africa. This technology has the potential to save the lives of 178 000 African children each year if implemented continent-wide.

Dr Sam Agbo, Head of Health, Save the Children said: 'This Award provides a platform for working in collaboration, which will ultimately help to save the lives of some of the world's most vulnerable children.'

The winners will be announced in December 2014.

Dengue vaccine moves a step closer

A new vaccine that can halve the number of dengue cases provides a welcome shot to fight a deadly disease that infects around 390 million people every year in the tropics.

Sanofi Pasteur, the pharmaceutical company that sponsored the development of the vaccine, has announced that it will be commercially available by July 2015.

At present, no licensed vaccine is available to prevent dengue, a mosquito-borne disease. This is the first dengue vaccine to reach phase 3 trial, the last stage of clinical testing, according to a study in the British medical journal *The Lancet* (11 July). Whilst only available against three of the four serotypes of Dengue virus, it is seen as a significant step forward.

The phase 3 trial was conducted in South-East Asia that accounts for 70% of the global dengue burden. The results showed an overall vaccine efficacy with a 56% reduction of dengue fever incidence, and 80% reduction of serious cases. The vaccine is also safe to use as recipients did not suffer from any vaccine-related health complications, the results showed.

Low birth weight link to diabetes

African women are at an increased risk for type 2 diabetes as they are often born at low birth weights a new study in *Diabetes Care* suggests.

The findings may partly explain high diabetes rates among black Americans, a population that has a high prevalence of low birth weight, the researchers added.

Their study of more than 21 000 black women found that those with a low birth weight were 13% more likely to develop type 2 diabetes than those with a normal birth weight. The risk of diabetes was 40% higher in those with a very low birth weight. Low birth weight was defined as less than 5.5 pounds and very low birth weight as less than 3.3 pounds.

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New eye clinic to serve two million: A groundbreaking ceremony for the new Invicta Eye Clinic in the Central Hospital in Beira, Mozambique, will serve as eye-care hub for two million people.

'Healthcare is a key factor in socioeconomic development. At Invicta Eye Clinic, we will be able to perform 1200 surgeries and treat a total of 25 000 patients per year', Prof. Gerhard Schuhmann, ophthalmologist from Austria and board member of LIGHT FOR THE WORLD said at the ceremony. The new clinic is named after Peter von Bertalanffy's Invicta foundation, who both contributed significantly to the project.

The concept for the new eye clinic reflects this: it will house training facilities that will enable the graduation of ten eye care professionals every two years. 'We are very proud that the Invicta Eye Clinic will be the first training centre of its kind outside of the capital Maputo', Zacharias Zicai said.

LIGHT FOR THE WORLD has been active in Mozambique since 2003. In cooperation with Beira Central Hospital the organisation is implementing a comprehensive blindness prevention programme for Central and Northern Mozambique, including outreach programmes, primary eye care units and professional trainings. LIGHT FOR THE WORLD and its programmes form part of the Vision2020 initiative aiming to eliminate preventable blindness globally by 2020. (http://www.light-for-the-world.org)

Algeria sees huge progress in ophthalmic services

At the end of the Algerian war, in 1962, there were only five ophthalmologists in the whole country. Since then, Algeria has gone through a large reorganisation, established a national healthcare system, and greatly increased human resources in all branches of medicine.

'We are now 1500 ophthalmologists, which is undoubtedly a great progress. Nevertheless, this number is not yet sufficient to serve a population of 38 million. We are far from covering the needs of our patients,' Boualem Chachoua, MD, president of the national association of private ophthalmologists, said.

'At high school, only seven were Algerians in my class; the rest were French. Our parents were poor, and only a small minority could afford to pay for us to go to university, and access was mostly denied to us. You had to fight your way through by showing the very best results at school to be admitted. When I entered university in 1966, Algerian students were around 1000 in the whole country,' Chachoua said.

Opening up the data highway

New statistical and open data platforms are being set up to remedy long-standing challenges of development data access across Africa, promising to improve services and increase transparency.

Open data in developing countries can be used 'to improve the efficiency and coverage of public services in a variety of development sectors such as education, health, transport, energy', says Amparo Ballivian, a lead economist at the World Bank.

'Open data can also help generate new businesses and therefore job opportunities, and improve transparency.'

In February, the African Development Bank (AfDB) launched the Africa Information Highway (AIH), which comprises two types of portals for each participating country: a statistical data portal and an open data portal.

'The AIH provides a vehicle for greater dissemination and faster access to these data. However, the AfDB is clearly interested in improving data quality.'

Statistical data portals contain official national statistical data that are 'disseminated and controlled by national statistics offices', says Ivo Njosa, lead consultant for the initiative at the AfDB.

'Open data portals contain data from national and other sources (such as the World Health Organization, the World Bank, or the UN) and allow users to create and share content directly on the open data (portal) or through social networks,' he says.

AIH is Africa's new 'one-stop centre' for development data, says Njosa.

'It was developed in response to data access challenges (facing) governments, policymakers, research institutions, private-sector organisations and ordinary African citizens,' he adds.

There are plans for capacity building workshops in November, which aim to unite governmental representatives from all African countries in one location, to emphasise the importance of data quality, he adds.

Since its launch, the AIH has seen increases in its usage, both from within African nations and from abroad. The most recent published report shows Mozambique's statistical data portal is the most visited, with 2620 visits during June, 59% of which came from within the country.

As part of the AIH's capacity building initiative, staff from the statistics offices of each country were trained on the use and maintenance of their portals.

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Medic emergence

Two big international medical exhibitions on opposite sides of the continent, take place in September and October. Bryan Pearson previews

Photo from the Medic East Africa exhibition last year

Photo from the Medic West Africa exhibition last year

We started Medic Africa back in 1986, it was the first formal trade show for the healthcare profession, and ran in the Banquet hall (and balcony) of the Eko Hotel. The first event had 15 exhibitors. We manufactured the stands via some aluminium poles which we procured from the Kaduna Furniture and Carpet Company, and my long-standing colleague Dr Adewale Balogun crafted wooden panels out of 16mm plywood. Nearly 30 years on, the scene has developed dramatically, we've also teamed up with Informa plc, global leaders at such events, and our biggest challenge now is finding venues big enough to accommodate the meetings.

First up this year is Medic East Africa in Nairobi. Last year we filled the Kenyatta International Conference Centre (KICC) and this year, to provide the extra space needed, we've moved to the recently built Visa Oshwal Centre in Westlands, close to several leading hospitals. The event takes place from 23 – 25th September and the Cabinet Secretary for Health, James Macharia is expected to preside over the opening. The exhibition of medical products is already 50% bigger than last year, cementing Nairobi's key role as the commercial health hub for the region.

Following on from this meeting, the caravan crosses the continent for Medic West Africa, which will take place at the now hugely upgraded scene of its first showing, the Eko Hotel. We will use the old Banquet Hall, but the bulk of the meeting will take place in the new Eko Convention Centre Hall, built on what used to be a palm orchard alongside the hotel buildings. Medic West Africa continues to grow. It is now the biggest professional trade show in Lagos and also features a range of associated events with conferences covering key health management issues, the management of infectious diseases, a seminar on facilities management, as well as a planned round table of senior opinion leaders from across the spectrum of involvement to look at the lessons learned from the Ebola outbreak. That of course does make a big assumption that the outbreak has been controlled in Nigeria by that time…but fingers crossed it is the case.

To both meetings, registration is available online via the obvious URL options, they are free to attend for health professionals. The associated CPD-accredited conferences attract a small registration fee. The size of the events indicates how sophisticated healthcare is becoming in much of Africa, and how important industry now holds the region to be. Product ranges span the sector, from the high-end MRI technologies to simple solutions for rural interventions. We look forward to welcoming as may Africa Health readers to the meetings. Not least, it is always a good opportunity for me to meet with you and find out what you like or dislike about the journal!

Ebola: management guidelines

Being the World Health Organization's interim infection prevention and control guidance for care of patients with suspected or confirmed Filovirus Haemorrhagic fever in healthcare settings, with focus on Ebola

Key messages for infection prevention and control (IPC) to be applied in healthcare

- Strengthen and carefully apply standard precautions when providing care to ALL patients regardless of the signs and symptoms they present with.
- Isolate suspected or confirmed Hemorrhagic fever (HF) cases in single isolation rooms or cohort them in specific confined areas while rigorously keeping suspected and confirmed cases separate. Assure restricted access to these areas and dedicated equipment.
- Exclusively assign clinical and non-clinical personnel to HF patient care areas.
- Ensure that prior to entering the patient isolation rooms/areas, all visitors and healthcare workers (HCWs) rigorously use personal protective equipment (PPE) and perform hand hygiene as indicated in this document. PPE should include at least: gloves, gown, boots/closed shoes with overshoes (and mask and eye protection for splashes).
- Ensure safety of injections and phlebotomy procedures and management of sharps.
- Ensure regular and rigorous environmental cleaning, decontamination of surfaces and equipment, and management of soiled linen and of waste as indicated in this document.
- Ensure safe processing of laboratory samples from suspected or confirmed patients with HF.
- Ensure that the IPC measures indicated in this document are followed while handling dead bodies or human remains of suspected or confirmed patients with HF for post-mortem examination and burial preparation.
- Promptly evaluate, care for, and if necessary, isolate HCWs or any person exposed to blood or body fluids from suspected or confirmed patients with HF.

Introduction

This document provides a summary of infection prevention and control (IPC) measures for those providing direct and non-direct care to patients with suspected or confirmed cases of Filovirus haemorrhagic fever (HF), including Ebola or Marburg haemorrhagic fevers, in healthcare facilities (HCFs). It also includes some instructions and directions for those managing the implementation of IPC activities. These IPC measures should be applied not only by healthcare professionals but by anyone in direct contact with patients (e.g. visitors, family members, volunteers), as well as by those not in contact with patients, but potentially exposed to the virus through contact with the environment (e.g. cleaners, laundry, house-keepers, security).

This document represents a rapid update of the World Health Organization (WHO) 2008 'Interim Infection Control Recommendations for Care of Patients with Suspected or Confirmed Filovirus (Ebola, Marburg) Hemorrhagic Fever'. This update is based upon review of WHO and other international reference documents being used in the current Ebola outbreak (see references) and international experts' consensus.

Ebola is a severe illness caused by Ebola virus. (http://www.who.int/csr/disease/ebola/en/). It is highly infectious, rapidly fatal, with a death rate of up to 90%, but can be prevented. It is spread through direct contact with body fluids like blood, saliva, urine, sperm, etc. of an infected person, and by contact with contaminated surfaces or equipment, including linen soiled by body fluids from an infected person. The Ebola virus can be relatively easily eliminated with heat, alcohol-based products, and sodium hypochlorite (bleach), or calcium hypochlorite (bleaching powder) at appropriate concentrations.

If carefully implemented, IPC measures will reduce or stop the spread of the virus and protect HCWs and others. It is advised that in the affected area(s), a subcommittee for clinical case management is established;[1] as part of this committee, a coordinator(s) should be named to oversee adherence to the IPC measures in each HCF, and acts as a focal person to coordinate activities and advise. If available, this person should be the professional in charge of IPC in the HCF.

Case identification and detection, contact tracing and patient clinical assessment and management are not the object of this Guidance document and instructions can be found elsewhere.[1,2] However, regarding IPC measures to be implemented during interviews for contact tracing and case finding in the community, the following principles should be kept in mind: 1) shaking hands should be avoided; 2) a distance of more than one metre (about 3 feet) should be maintained between interviewer and interviewee; 3) PPE is not required if this distance is assured and when interviewing asymptomatic individuals (e.g. neither fever, nor diarrhoea, bleeding or vomiting) and provided there will be no contact with the environment, potentially contaminated with a possible/probable case; 4) it is advisable to provide workers undertaking contact tracing and case finding in the community with alcohol-based hand rub solutions and instructions to appropriately perform hand hygiene.

Médecins Sans Frontières doctors try to feed a young girl in the high contamination risk zone of the Ebola treatment centre in Kailahun, Sierra Leone. Photo credit: ©Sylvain Cherkaoui/Cosmos

1. General patient care

Strengthen and carefully apply standard precautions 2-4 when providing care to ALL patients regardless of the signs and symptoms they present with. This is especially important because the initial manifestations of HF may be non-specific. Hand hygiene is the most important measure. Gloves should be worn for any contact with blood or body fluid. Medical mask and goggles, or face shield should be used if there is any potential for splashes of blood or body fluids to the face, and cleaning of contaminated surfaces is paramount.

2. Direct patient care (for suspected or confirmed patients with HF)

Patient placement, staff allocation, visitors

- Put suspected or confirmed cases in single isolation rooms with an adjoining dedicated toilet or latrine, showers, sink equipped with running water, soap and single-use towels, alcohol-based hand rub dispensers, stocks of personal protective equipment (PPE), stocks of medicines, good ventilation, screened windows, doors closed and restricted access;[2] if isolation rooms are unavailable, cohort these patients in specific confined areas while rigorously keeping suspected and confirmed cases separate and ensure the items listed here for isolation rooms are readily available. Make sure that there is at least 1 meter (3 feet) distance between patient beds.
- Ensure that clinical and non-clinical personnel are assigned exclusively to HF patient care areas and that members of staff do not move freely between the HF isolation areas and other clinical areas during the outbreak.
- Restrict all non-essential staff from HF patient care areas.
- Stopping visitor access to the patient is preferred, but if this is not possible, limit their number to include only those necessary for the patient's well-being and care, such as a child's parent.
- Do not allow other visitors to enter the isolation rooms/areas and ensure that any visitors wishing to observe the patient do so from an adequate distance (approximately 15m or 50 feet).
- Before allowing visitors to HF patients to enter the HCF, screen them for signs and symptoms of HF.

Hand hygiene, personal protective equipment (ppe) and other precautions

- Ensure that all visitors use PPE and perform hand hygiene as indicated below and are provided with related instructions (Annex 1)[2,5,6] prior to entry into the isolation room/area.
- Ensure that all HCWs (including aides and cleaners) wear PPE (Annex 1) as appropriate according to the expected level of risk before entering the isolation rooms/areas and having contacts with the patients and/or the environment.
- Personal clothing should not be worn for working in the patient areas. Scrub or medical suits should be worn.
- Carefully apply the following precautions[3,7] to avoid any possible unprotected direct contact with blood and body fluids when providing care to any patient with HF, including suspected cases:

  Perform hand hygiene:

  - before donning gloves and wearing PPE on entry to the isolation room/area,
  - before any clean/aseptic procedures being performed on a patient,
  - after any exposure risk or actual exposure with the patient's blood and body fluids,
  - after touching (even potentially) contaminated surfaces/items/equipment in the patient's surroundings,
  - and after removal of PPE, upon leaving the care area.

Hand hygiene should be performed within the isolation rooms/areas every time it is needed according to the above indications during care to a patient, along with change of gloves. When caring for patients in the same room, it is essential to organise the complete care to each patient before moving to the next and to perform hand hygiene between touching the patients. Furthermore, neglecting to perform hand hygiene after removing PPE will reduce or negate any benefits of the protective equipment.

To perform hand hygiene, either use an alcohol-based hand rub or soap and running water applying the correct technique recommended by WHO.[5] Always perform hand hygiene with soap and running water when hands are visibly soiled. Alcohol-based hand rubs should be made available at every point of care (at the entrance and within the isolation rooms/areas) and are the standard of care. However, if alcohol-based hand rubs are unavailable, perform hand hygiene with soap and running water every time necessary according to the above indications. Alcohol-based hand rubs can be produced locally at the HCF level by following the WHO recommendations and instructions.[8]

Before entering the isolation rooms/areas, wear PPE in dedicated changing zone as follows:

- Correctly sized gloves (non-sterile examination gloves) when entering the patient care area.[6] Consider changing gloves if heavily soiled with blood or any body fluids while providing care to the same patient (perform careful hand hygiene

immediately after removal). Always change gloves and perform hand hygiene immediately after removal, when moving from one patient to another while caring for patients in the same room. Consider double gloving when the quality of gloves appears to be poor (e.g., if holes and tears form rapidly during use).
- A disposable, impermeable gown to cover clothing and exposed skin.
- A medical mask and eye protection (eye visor or goggles or face shield) to prevent splashes to the nose, mouth and eyes.
- Closed, puncture and fluid resistant shoes (e.g. rubber boots) to avoid contamination with blood or other body fluids or accidents with misplaced, contaminated sharp objects. If boots are not available, overshoes should be used but these must be removed while still wearing gloves and with caution to avoid hand contamination.

When undertaking any strenuous activity (e.g. carrying a patient) or tasks in which contact with blood and body fluids is anticipated (e.g. the patient has symptoms like diarrhoea, bleeding or vomiting and/or the environment could be contaminated with blood or body fluids), in addition to the above-mentioned PPE, also use double gloving, and wear a waterproof apron over the gown if for any reasons your gown is non-impermeable, and disposable overshoes and leg coverings, if boots are not available.

Avoid aerosol-generating procedures if possible. Wear a respirator (FFP2 or EN certified equivalent or US NIOSH-certified N95), if any procedures that stimulate coughing or promote the generation of aerosols (e.g. aerosolised or nebulised medication administration, diagnostic sputum induction, bronchoscopy, airway suctioning, endotracheal intubation, positive pressure ventilation via face mask) is planned to be performed.[7]

Before exiting the isolation room/area, carefully remove and dispose of PPE (including boots) into waste containers and perform hand hygiene.[2]

When removing PPE, be careful to avoid any contact between the soiled items (e.g. gloves, gowns) and any area of the face (i.e. eyes, nose or mouth) or non-intact skin.

Do not recycle any single-use disposable PPE. However, if the decontamination of goggles and visors is necessary, it is essential that these items should be cleaned with water (± detergent) to remove any organic matter and then immersed fully in 1000 ppm [parts per million] of available chlorine (0.5%) for a minimum of 30 mins (preferably overnight) for decontamination. After decontamination, they should be thoroughly rinsed with water (to remove irritating hypochlorite residues and salt deposits) before re-use. The wipes used for the initial cleaning should be treated as infectious waste; the disinfectant can be safely poured down a sink or drain.[9]

Carefully clean and decontaminate reusable equipment. Rigorously use dedicated equipment (e.g. stethoscopes) for each patient. However, if this is not possible, decontaminate the items between each patient contact. For instance, if the stethoscope has to be used on different patients, it is essential that the full stethoscope (i.e. staff hand contact as well as patient contact surfaces) be thoroughly cleaned first with water and soap using appropriate PPE to remove organic matter and then wiped with alcohol.[9] All waste generated during this decontamination process should be treated as infectious waste.

Items and equipment should not be moved between isolation rooms/areas and other areas of the HCF, unless they are appropriately discarded and disposed. For instance, the patient charts and records should be kept outside the isolation rooms/areas to avoid their contamination.

Injection safety and management of sharps

- Each patient should have exclusively dedicated injection and parenteral medication equipment which should be disposed of at the point of care. Syringes, needles or similar equipment should never be reused.
- Limit the use of needles and other sharp objects as much as possible.
- Limit the use of phlebotomy and laboratory testing to the minimum necessary for essential diagnostic evaluation and patient care.[9]
- If the use of sharp objects cannot be avoided, ensure the following precautions are observed:[10]
  - Never replace the cap on a used needle.
  - Never direct the point of a used needle to wards any part of the body.
  - Do not remove used needles from disposable syringes by hand, and do not bend, break or otherwise manipulate used needles by hand.
  - Dispose of syringes, needles, scalpel blades and other sharp objects in appropriate, puncture-resistant containers.
- Ensure that puncture-resistant containers for sharps objects are placed as close as possible to the immediate area where the objects are being used ('point of use') to limit the distance between use and disposal, and ensure the containers remain upright at all times. If the sharps container is far, never carry sharps in your hand but place them all in a kidney dish or similar to carry to the sharps container.
- Ensure that the puncture-resistant containers are securely sealed with a lid and replaced when 3/4 full.
- Ensure the containers are placed in an area that is not easily accessible by visitors, particularly children (e.g. containers should not be placed on floors, or on the lower shelves of trolleys in areas where children might gain access).

3. Environmental cleaning and management of linen

PPE

- Wear heavy duty/rubber gloves, impermeable gown and closed shoes (e.g. boots) when cleaning the environment and handling infectious waste.
- In addition, wear facial protection (mask and goggle or face shield) and overshoes if boots are unavailable, when undertaking cleaning activities with increased risk of splashes or in which contact with blood and body fluids is anticipated (e.g. cleaning surfaces heavily soiled with vomit or blood or cleaning areas closer than 1 meter/3 feet from a patient with symptoms like diarrhoea, bleeding or vomiting, etc.).

Cleaning process

- Environmental surfaces or objects contaminated with blood, other body fluids, secretions or excretions should be cleaned and disinfected as soon as possible using standard hospital detergents/ disinfectants (e.g. a 0.5% chlorine solution or a solution containing 1000 ppm available free chlorine).[11] Application of disinfectants should be preceded by cleaning to prevent inactivation of disinfectants by organic matter.
- If locally prepared, prepare cleaning and disinfectant solutions every day. Change cleaning solutions and refresh equipment frequently while being used during the day, as they will get contaminated quickly (follow your hospital protocols if available).
- Clean floors and horizontal work surfaces at least once a day with clean water and detergent. Cleaning with a moistened cloth helps to avoid contaminating the air and other surfaces with air-borne particles. Allow surfaces to dry naturally before using them again.
- Dry sweeping with a broom should never be done. Rags holding dust should not be shaken out and surfaces should not be cleaned with dry rags.
- Cleaning should always be carried out from 'clean' areas to 'dirty' areas, in order to avoid contaminant transfer.
- Do not spray (i.e. fog) occupied or unoccupied clinical areas with disinfectant. This is a potentially dangerous practice that has no proven disease control benefit.

Management of linen

- Linen that has been used on patients can be heavily contaminated with body fluids (e.g. blood, vomit) and splashes may result during handling. When handling soiled linen from patients, use gloves, gown, closed shoes (e.g. boots) and facial protection (mask and goggle or face shield).
- Soiled linen should be placed in clearly-labelled, leak-proof bags or buckets at the site of use and the container surfaces should be disinfected (using an effective disinfectant) before removal from the isolation room/area. If there is any solid excrement such as faeces or vomit, scrap off carefully using a flat firm object and flush it down the toilet or in the sluice before linen is placed in its container. If the linen is transported out of the patient room/area for this procedure it should be put in a separate containter – it should never be carried against the body.
- Linen should be then transported directly to the laundry area in its container and laundered promptly with water and detergent.
- For low-temperature laundering, wash linen with detergent and water, rinse and then soak in 0.05% chlorine for approximately 30 minutes. Linen should then be dried according to routine standards and procedures.
- Washing contaminated linen by hand should be discouraged. However, if washing machines are not available or power is not ensured, take the soiled linen out of the container and empty it into a large drum container of hot water and soap. Soak the linen in this drum and make sure it is totally covered with water. Use a stick to stir; then throw out the water and refill the drum with clean water and add bleach 1000ppm and allow to soak for 10-15 minutes. Remove the linen and then rinse in clean water. Remove excess water and spread out to dry. Avoid as much splashing as possible.
- If safe cleaning and disinfection of heavily soiled linen is not possible or reliable, it may be prudent to burn the linen to avoid any unnecessary risks to individuals handling these items.

4. Waste management

PPE

- Wear heavy duty/rubber gloves, impermeable gown, closed shoes (e.g. boots) and facial protection (mask and goggle or face shield), when handling infectious waste (e.g. solid waste or any secretion or excretion with visible blood even if it originated from a normally sterile body cavity). Goggles provide greater protection than visors from splashes that may come from below when pouring liquid waste from a bucket. Avoid splashing when disposing of liquid infectious waste.

Waste management procedures

- Waste should be segregated at point of generation to enable appropriate and safe handling.
- Sharp objects (e.g. needles, syringes, glass articles) and tubing that has been in contact with blood or body fluids should be placed inside puncture resistant waste containers (as described above). These should be located as close as practical to the patient care area where the items are used, similarly in laboratories.
- Collect all solid, non-sharp, infectious waste using leak-proof waste bags and covered bins. Bins should never be carried against the body (e.g. on the shoulder).
- Waste should be placed in a designated pit of appropriate depth (e.g. 2m or about 7 feet) and filled to a depth of 1-1.5m (or about 3-5 feet). After each waste load, the waste should be covered with a layer of soil 10 -15cm deep.
- An incinerator may be used for short periods during an outbreak to destroy solid waste. However, it is essential to ensure that total incineration has taken place. Caution is also required when handling flammable material and when wearing gloves due to the risk of burn injuries if gloves are ignited.
- Placenta and anatomical samples should be buried in a separate pit.
- The area designated for the final treatment and disposal of waste should have controlled access to prevent entry by animals, untrained personnel or children.
- Waste, such as faeces, urine and vomit, and liquid waste from washing, can be disposed of in the sanitary sewer or pit latrine. No further treatment is necessary.

Summary table for implementation of IPC best practices during direct patient care and related activities

What?	How?	Who is responsible?
Create isolation rooms or areas.	- Identify single rooms and prioritise these for patients with known or suspected Ebola virus. - Refer to guidance on setting up an isolation area.[2]	- Coordinator or IPC staff to identify areas/rooms for patient placement. - Health workers to adhere to recommendations and report to the coordinator when a patient is not placed in an isolation room/area.
Restrict all non-essential staff from HF patient care rooms/areas.	- Ensure that clinical and non-clinical personnel are assigned exclusively to patient care areas and that members of staff do not move freely between these areas and other clinical areas during the outbreak. - Cohort staff between areas with suspected and those with confirmed HF patients. - Use signage to alert restrictions of staff.	- Coordinator and/or IPC staff.
Limit the number of visitors allowed access to the patient.	- Use signage and other communications to alert restrictions of visitors. Make simple messages understandable for the public but also be careful to avoid stigmatisation.	- Coordinator and/or IPC staff - Involve patient or community representatives, if available. - Health workers to adhere to recommendations and report to the coordinator when they are not followed.
Ensure that all staff and visitors correctly use and remove recommended personal protective equipment (PPE).	- Ensure the equipment is always available and promptly at the isolation rooms/areas entry. - Provide staff and visitors with instructions on the use and correct removal of PPE through training and reminder posters.	- Coordinator and/or IPC staff - Involve patient or community representatives, if available. - Health workers to adhere to recommendations and report to the coordinator when they are not followed. - Another staff member should be assigned to supervise the sequence of putting on and removing PPE by his/her colleague.
Ensure that all staff and visitors perform hand hygiene according to the above recommendations. These hand hygiene actions should be performed when recommended even if PPE is worn.	- Provide staff and visitors with instructions on the importance of hand hygiene best practices through training and reminder posters. - Ensure continuous availability of alcohol-based handrub and soap, water and single-use towels at the isolation room/areas entry and at the point of care.	- Coordinator and/or IPC staff. - Involve patient or community representatives, if available. - Health workers to adhere to recommendations and report to the coordinator when they are not followed.
Limit the use of needles and other sharp objects as much as possible. If this cannot be avoided see instructions in the text.	- Provide staff and carers with instructions on the essential use of needles and sharps through training and reminder posters. - Ensure the equipment is available to do this.	- Health workers to adhere to recommendations.

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What?	How?	Who is responsible?
Dispose of needles and other sharp objects safely.	- Provide staff and carers with instructions on the safe disposal of sharps through training and reminder posters. - Ensure the equipment is available to do this.	- Health workers to adhere to recommendations and report to the coordinator when they are not followed.
Create system of safe management of waste and linen.	- Provide staff and visitors/carers with instructions on the safe management and disposal of waste and linen through training and reminder posters. - Ensure the equipment is available to do this.	- Health workers to adhere to recommendations and report to the coordinator when they are not followed.
Limit the use of phlebotomy and laboratory testing to the minimum necessary for essential diagnostic evaluation and patient care.	- Provide staff with training and visual instructions on the need for essential phlebotomy and lab testing.	- Health workers to adhere to recommendations.
Only take a patient out of their room/ care area if they are free of virus, or for essential, life-saving tests.	- Provide staff with training and visual instructions on the appropriate times to take the patient from their care area and on precautions to take.	- Health workers to adhere to recommendations and report to the coordinator when they are not followed.
Undertake cleaning of the environment and patient care equipment safely following recommendations in the text.	- Provide staff and visitors/ carers with instructions on cleaning through training and reminder posters. - Ensure the equipment is available to undertake recommended cleaning.	- Health workers to adhere to recommendations and report to the coordinator when they are not followed.

IPC = infection prevention and control; PPE = personal protective equipment

5. NON-PATIENT CARE ACTIVITIES (FOR SUSPECTED OR CONFIRMED PATIENTS WITH HF)

A. Diagnostic laboratory activities

- For procedures to safely collect blood or other samples from persons suspected or confirmed to be infected, follow the instructions provided by WHO.[9]
- All laboratory sample processing must take place under a safety cabinet or at least a fume cabinet with exhaust ventilation. Do not carry out any procedure on the open bench.
- Activities such as micro-pipetting and centrifugation can mechanically generate fine aerosols that might pose a risk of transmission of infection through inhalation as well as the risk of direct exposure.
- Laboratory personnel handling potential HF clinical specimens should wear closed shoes with overshoes or boots, gloves, a disposable, impermeable gown, eye protection or face shields, and particulate respirators (e.g. FFP2, or EN certified equivalent, or US NIOSH-certified N95), or powered air purifying respirators (PAPR) when aliquotting, performing centrifugation or undertaking any other procedure that may generate aerosols.
- When removing PPE, avoid any contact between the soiled items (e.g. gloves, gowns) and any area of the face (i.e. eyes, nose or mouth).
- Do not hang up the apron or gown for reuse - discard immediately.
- Perform hand hygiene immediately after the removal of PPE used during specimen handling and after any contact with potentially contaminated surfaces even when PPE is worn.
- Place specimens in clearly-labelled, non-glass, leak-proof containers and deliver directly to designated specimen handling areas.
- Disinfect all external surfaces of specimen containers thoroughly (using an effective disinfectant) prior to transport.

B. Movement and burial of human remains

- The coordinator and/or the infection prevention and control staff should be consulted for any decision making on movement and burial of human remains.
- For this topic, see also the WHO 'Interim manual - Ebola and Marburg virus disease epidemics: preparedness, alert, control, and evaluation'.[1]

- The handling of human remains should be kept to a minimum. The following recommendations should be adhered to in principle, but may need some adaptation to take account of cultural and religious concerns:
  - Wear PPE (impermeable gown, mask, eye protection and double gloves) and closed shoes or boots to handle the dead body of a suspected or confirmed case of HF. Plug the natural orifices. Place the body in a double bag, wipe over the surface of each body bag with a suitable disinfectant (e.g. 0.5% chlorine solution) and seal and label with the indication of highly-infectious material. Immediately move the body to the mortuary.
  - PPE should be put on at the site of collection of human remains, worn during the process of collection and placement in body bags, and should be removed immediately after. Hand hygiene should be performed immediately following the removal of PPE.
  - Remains should not be sprayed, washed or embalmed. Any practice of washing the remains in preparation of 'clean burials' should be discouraged.
  - Only trained personnel should handle remains during the outbreak.
  - PPE is not required for individuals driving or riding a vehicle to collect human remains, provided that drivers or riders will not be handling a dead body of a suspected or confirmed case of HF.
  - After wrapping in sealed, leak-proof material, remains should be placed inside a coffin if possible, and buried promptly.

C. Post-mortem examinations

- The coordinator and/or the IPC staff should be consulted for any decision making on post-mortem examinations.
- Post-mortem examination of HF patient remains should be limited to essential evaluations only and should be performed by trained personnel.
- Personnel examining remains should wear eye protection, mask, double gloves, disposable, impermeable gowns, and closed shoes or boots.
- In addition, personnel performing autopsies of known or suspected HF patients should wear a particulate respirator (e.g. FFP2, or EN certified equivalent, or US NIOSH-certified N95) or a PAPR.
- When removing PPE, avoid any contact between soiled gloves or equipment and the face (i.e. eyes, nose or mouth).
- Hand hygiene should be performed immediately following the removal of PPE.
- Place specimens in clearly-labelled, non-glass, leak-proof containers and deliver directly to designated specimen handling areas.
- All external surfaces of specimen containers should be thoroughly disinfected (using an effective disinfectant) prior to transport.
- Tissue or body fluids for disposal should be carefully placed in clearly marked, sealed containers for incineration.

D. Managing exposure to virus through body fluids including blood

- Persons including HCWs with percutaneous or muco-cutaneous exposure to blood, body fluids, secretions, or excretions from a patient with suspected or confirmed HF should immediately and safely stop any current tasks, leave the patient care area, and safely remove PPE. Remove PPE carefully because exposure during PPE removal can be just as dangerous for nosocomial transmission of HF. Immediately after leaving the patient care area, wash the affected skin surfaces or the percutaneous injury site with soap and water. Accordingly, irrigate mucous membranes (e.g. conjunctiva) with copious amounts of water or an eyewash solution, and not with chlorine solutions or other disinfectants.
- Immediately report the incident to the local coordinator. This is a time-sensitive task and should be performed as soon as the HCW leaves the patient care unit.
- Exposed persons should be medically evaluated including for other potential exposures (e.g. HIV, HCV) and receive follow-up care, including fever monitoring, twice daily for 21 days after the incident. Immediate consultation with an expert in infectious diseases is recommended for any exposed person who develops fever within 21 days of exposure.
- HCWs suspected of being infected should be cared for/isolated, and the same recommendations outlined in this document must be applied until a negative diagnosis is confirmed.
- Contact tracing and follow-up of family, friends, co-workers and other patients, who may have been exposed to Ebola virus through close contact with the infected HCW is essential.

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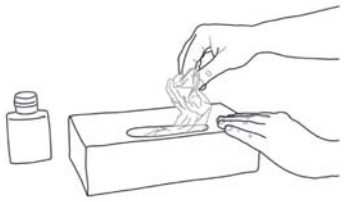
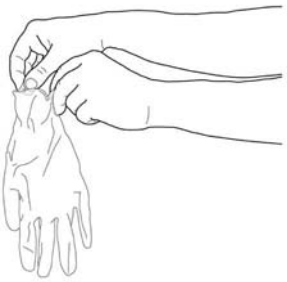
Annex 1: Technique for donning and removing non-sterile examination gloves

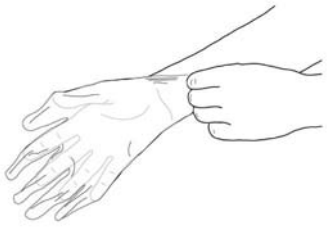
1. How to don gloves:



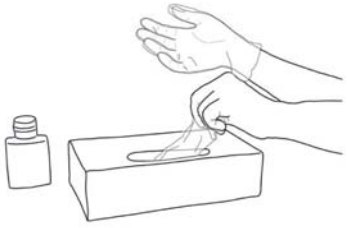
1. Take out a glove from its original box



2. Touch only a restricted surface of the glove corresponding to the wrist (at the top edge of the cuff)

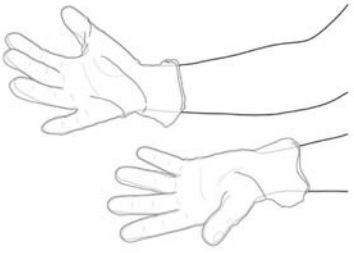


3. Don the first glove



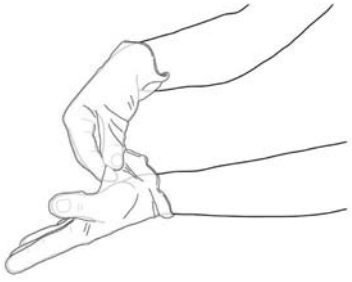
4. Take a second glove with the bare hand and touch only a restricted surface of glove corresponded to the wrist

5. To avoid touching the skin on the forearm with the gloved hand, turn the external surface of the glove to be donned on the folded fingers of the gloved hand, thus permitting to glove the second hand

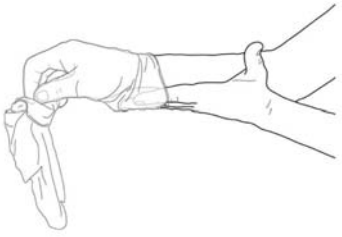


6. Once gloved, hands should not touch anything else that is not defined by indications and conditions for glove use

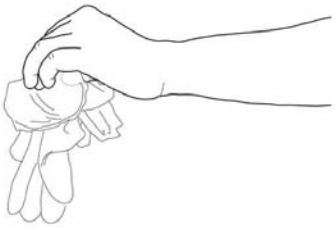
2. How to remove gloves:



1. Pinch one glove at the wrist level to remove it, without touching the skin on the forearm, and peel away from the hand, thus allowing the glove to turn inside out



2. Hold the removed glove in the gloved hand and slide the fingers of the ungloved hand inside between the glove and the wrist. Remove the second glove by rolling it down the hand and fold into the first glove



3. Discard the removed gloves

4. Then, perform hand hygiene by rubbing with an alcohol-based handrub or by washing with soap and water

Source: Glove Use Information Leaflet. World Health Organization, Geneva, 2009. Available from: http://www.who.int/gpsd5may/tools/training_educational/en/

Children matter

77% of those who die from malaria are children under 5

That's **483,000** young lives lost every year

or **one child every minute**

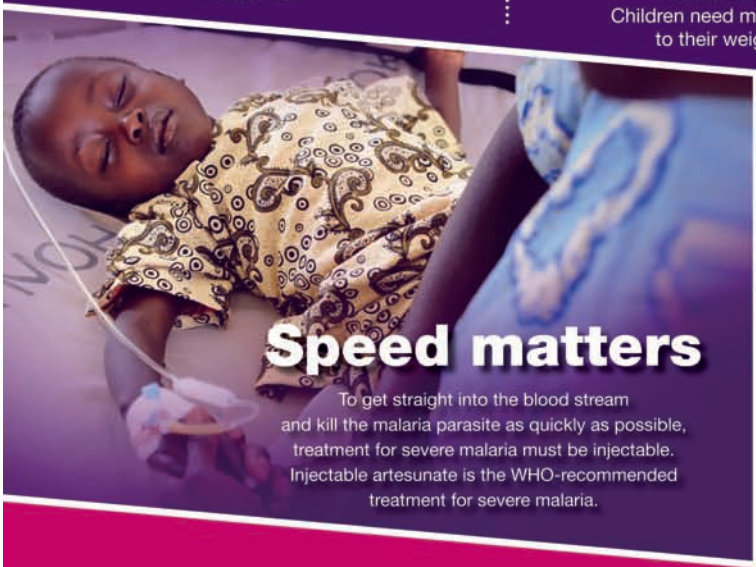
Medicines matter

We need new medicines for children, to cure them and counter drug resistance because...

Severe malaria can kill within 24 hours, without appropriate treatment.

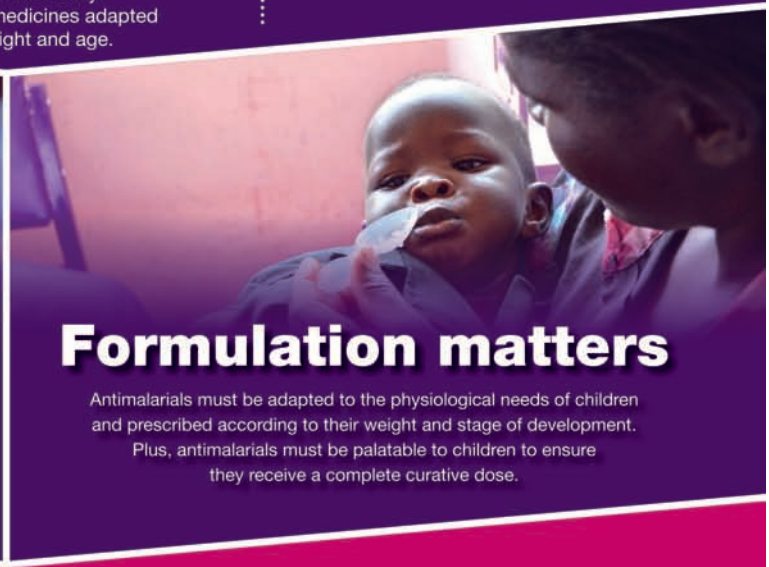
Children are not just little adults. They absorb and metabolize medicines differently. Children need medicines adapted to their weight and age.

Antimalarials are bitter. Children often vomit the medicine and so do not receive a complete curative dose.



Speed matters

To get straight into the blood stream and kill the malaria parasite as quickly as possible, treatment for severe malaria must be injectable. Injectable artesunate is the WHO-recommended treatment for severe malaria.



Formulation matters

Antimalarials must be adapted to the physiological needs of children and prescribed according to their weight and stage of development. Plus, antimalarials must be palatable to children to ensure they receive a complete curative dose.

MMV's response

Artesun®[1] for severe malaria

Since WHO prequalification, 12 million vials delivered, saving an estimated 80,000-90,000 additional lives compared to quinine

Coartem®[2] *Dispersible*

200 million treatments of this child-friendly medicine delivered to 50 countries

Eurartesim®[3] and Pyramax®[4] paediatric formulations

2 new medicines being adapted to children's needs

1. artesunate for injection
2. artemether-lumefantrine
3. dihydroartemisinin-piperaquine
4. pyronaridine-artesunate

Defeating Malaria Together

MMV Medicines for Malaria Venture

From famine to feast: the transformation of the ACT malaria treatment landscape since 2004

Medicines for Malaria Venture and Drugs for Neglected Diseases initiative explore the advantages of multiple ACTs for malaria and how to prolong their usefulness

'As doctors, we want to use effective treatments. We cannot continue prescribing a first-line malaria treatment – such as sulfadoxine-pyrimethamine - which we know is not going to cure the patient.'
Médecins Sans Frontières, 2002

As little as 10 years ago, owing to drug resistance, a clinician treating a patient for malaria would be routinely confronted with a terrible dilemma: 'Will the drug I prescribe actually cure my patient?' Between 1999 and 2002, rates of resistance to chloroquine and sulfadoxine-pyrimethamine (SP) in excess of 90% and up to 60%, respectively, were being reported in parts of East Africa.[1] This dire situation continued until World Health Organization's (WHO) prequalification of the first artemether-lumefantrine (AL) artemisinin combination therapy (ACT) in 2004, followed by growing support from donors for the large-scale introduction of ACTs. By 2005, 40 countries had adopted ACT[2] as either first or second-line therapy and their distribution broke through the 10 million treatment mark and steadily increased over the next eight years, spurred on by the development of new fixed-dose combinations.

By 2012, 79 countries and territories had adopted ACT as first-line treatment for uncomplicated malaria.[3] Almost 200 million ACTs were procured for use by public health systems in 2013, with around another 150 million treatments procured for use in the private sector, primarily in price-subsidised schemes.[4] WHO guidelines today recommend the use of five different ACT options, four of which are available in fixed-dose combination - strongly preferred by WHO over co-blistered combination therapies, as they 'promote adherence to treatment and reduce the potential selective use of the medicines as monotherapy.' [5] This dramatic increase in the availability and diversification of treatment options represents a unique moment in the history of malaria treatment. While there are worrisome signs of the limited spread of artemisinin resistance in the Greater Mekong sub-region in Southeast Asia, there is no sign yet of artemisinin resistance in Africa.[6]

Accordingly, African countries may be able to rely on these effective medicines for several years to come.

Combination**	**Manufacturer(s)** and year prequalifyied or SRA-approved*	**Fixed dose (FDC) or loose**
Artemether-Lumefantrine (AL)	Novartis (2004-tablet; 2009-dispersible)	FDC
	Ajanta (2008-tablet; 2012-dispersible)	FDC
	Ipca (2009-tablet)	FDC
	Cipla (2009-tablet)	FDC
	Strides (2013-tablet)	FDC
	Macleods (2013-tablet)	FDC
	Mylan (2014-tablet)	FDC
Artesunate-Amodiaquine (AS-AQ)	Guilin (2007-co-blistered, 2012-FDC)	FDC
	Sanofi (2008)	FDC
	Ipca (2008-co-blistered; 2012-FDC)	FDC
	Ajanta (2013)	FDC
	Strides (2011)	Co-blistered
	Cipla (2008-co-blistered; 2014-FDC)	FDC
Dihydroartemisinin + Piperaquine (DHA-PQP)	Sigma Tau (2011)*	FDC
Artesunate + Mefloquine (AS-MQ)	DNDi / Cipla (2012)	FDC
Artesunate + [Sulfadoxine + Pyrimethamine] (AS-SP)	Guilin (2012)	Loose
* SRA: Stringent Regulatory Authority; EMA marketing authorisation; FDC: Fixed Dose Combination		
** Not listed: Pyronaridine Artesunate, by Shin Poong Pharma. While this drug has been granted a positive scientific opinion by the EMA Article 58 review process and is listed on WHO's prequalified drug list, the drug is not yet included as a recommended treatment in the WHO Standard Treatment Guidelines.		

Table 1. WHO-recommended ACT treatments for uncomplicated malaria. [7]

Today, there are five distinct combinations of partner drugs with artemisinin (Table 1). This comparative diversity of ACTs confers multiple advantages for global strategies to combat malaria:

(a) Differentiated use of ACTs for complementary interventions. While all the ACTs listed have been developed to treat uncomplicated malaria, in the past three years there has been a growing interest in additional therapeutic interventions as part of national malaria control programming. For example, to avoid lighting the fire of drug resistance to medicines used for treatment, several countries have selected a different ACT for mass drug administration or chemoprevention studies than is used for treatment.[8,9,10]

In the Sahel region, seasonal malaria chemoprevention (SMC) is currently being scaled-up. SMC uses a loose combination of SP+Amodiaquine (AQ) rather than an ACT but, in areas where it is deployed, WHO states that alternative antimalarials containing neither SP nor AQ must be used for the treatment of uncomplicated malaria.[11] Thanks to the availability of alternative ACTs for uncomplicated acute malaria, SMC offers the potential to save thousands of children's lives in West Africa.

(b) Increased patient/provider choice and adaptation for patient sub-populations. Having several quality treatment options is not only a boon for healthcare professionals but also for patients, who often buy their medicines from private drug sellers where they select which ACT to take. As such, increasing the choice of quality medicines available in the private sector may improve the likelihood that an effective ACT will be selected.

Although all of the ACTs listed are considered effective for uncomplicated malaria, formulation and dosing differences may make some more useful for specific sub-populations. For example, a pleasant-tasting dispersible paediatric formulation or a single daily dose versus a twice a day treatment may be particularly well suited to a rural/community delivery programme where thinly spread healthcare workers may not be able to monitor treatment adherence.

(c) Strengthening options for alternative first- and second-line treatments for uncomplicated malaria. Sometimes, for unclear reasons (e.g. incomplete dosing), a patient is not completely cured after a course of treatment. Given the potentially life-threatening nature of the infection, healthcare workers must determine, with imperfect information, if a second round of treatment is necessary. In this situation, it is critical to have an effective second-line course of treatment.

(d) Diversifying first-line treatment options through different supply chains. In 2007, Ghana pioneered a national malaria treatment policy that *de facto* embraced the concept of multiple first-line therapies' (MFL).[12] Three different ACTs (AL, DHA-PQP, AS-AQ) were approved as interchangeable first-line medicines for the treatment of uncomplicated malaria. In practical terms, Ghanaian officials determined that the public sector system would dispense AS-AQ and AL, and that private sector outlets would offer patients DHA-PQP as the third approved ACT option. Today, as more countries are registering prequalified versions of different ACTs, their ability to explore variations on the Ghanaian experience becomes more feasible.

(e) Enhancing stock security through a diversified base of suppliers. Public health planners generally prefer to have multiple options for the manufacture and supply of essential medicines worldwide. Reliance on one or two manufacturers creates vulnerability for the global supply chain, as any disruption for a single company can become a global public health crisis. Diversification in supply not only diminishes the chances of major disruptions in the supply chain but also, thanks to increased competition, can help to increase drug affordability.

(f) Keeping resistance at bay. While African countries should be able to count on continued efficacy of today's ACTs for many years to come, at some point, artemisinin resistance will emerge and spread. WHO's recommendations for parts of Southeast Asia[13] have included switching between different ACTs in areas of identified drug resistance in recent years. Thus, it may be that having a wide variety of ACT combinations today will help buy time when resistance comes knocking in Africa.[14]

The way forward

Today's global pharmacopeia for uncomplicated malaria contains more therapeutic options than at any point in history. Today, WHO recommends five distinct ACT combinations. With the potential broader introduction of pyronaridine-artesunate as a new ACT in 2015-2016, that figure could rise to six. It is a remarkable time. Continuing technological advances - such as the shift towards semi- and fully-synthetic artemisinins to reduce dependence on agriculture, and the likely introduction of single-dose cures in the next few years - will help contribute to the eventual elimination of this human scourge. Meanwhile, to prolong the usefulness of ACTs, key areas for action include:

1. Exploring new ways to utilise today's wide range of ACTs. For example, countries could choose to emulate the example of Ghana in rolling out MFL adapted to their settings.
2. Continuing to document and publish evidence from modelling and simulations that may build stronger evidence regarding how to optimally use an increasing array of anti-malarial medicines.
3. Constant monitoring for signs of emerging drug resistance; the earlier it can be detected, the sooner an informed decision can be made to switch to an alternative ACT. The discovery of a molecular marker of artemisinin resistance is an important breakthrough in helping ensure the longevity of this drug class[15] and new tools should allow reductions in parasite susceptibility to be detected earlier.[16]
4. Maintaining a global focus on addressing the manufacture and distribution of counterfeit and sub-standard ACTs – fake medicines threaten patient health and accelerate the decline of the ACT class of therapies.

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Conclusion

Almost 10 years ago, African countries began a major transformation of malaria treatment protocols in favour of ACTs, turning away from failed treatment regimens based on SP and chloroquine. Since then, ACTs have contributed enormously by providing fast and effective cures for uncomplicated malaria, with over 1.5 billion treatments distributed.[2] Given the approximate 95% efficacy of WHO-prequalified ACTs in providing a complete cure for uncomplicated malaria, the life-saving impact of ACTs has been massive.[17]

In the future, the next therapeutic revolution will be simpler, single-dose cures for malaria. Until then, the wealth of ACTs available today should continue to serve the evolving needs and demands of African malaria control programmes with greater versatility than has ever been possible in the history of malaria control. Wise drug policies can preserve the efficacy of the ACTs throughout Africa and beyond, and can ensure an effective arsenal of these medicines for many years to come.[18]

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Saving more lives from severe malaria

New evidence demonstrates the life-saving impact and feasibility of switching to injectable artesunate for the treatment of severe malaria

Around 5.6 million people fall prey to severe malaria every year, leading to an estimated 627 000 deaths, mostly of children under five years of age.[1] The results of two large-scale clinical studies, published in 2005 and 2010, demonstrated the clear superiority of injectable artesunate for the treatment of severe malaria over quinine, the previous standard of care. In Asia, a 34.7% reduction in mortality resulted when injectable artesunate was used instead of intravenous quinine in adults, while in African children, a comparable study showed a 22.4% reduction.[2,3] Based on this research, the World Health Organization (WHO) updated its standard treatment guidelines in 2011, recommending injectable artesunate as the preferred treatment for severe malaria. Médecins Sans Frontières (MSF) estimates that approximately 200 000 additional lives could be saved each year if malaria-endemic countries made the switch to injectable artesunate.[4]

Joining forces to make the switch

In response to this body of evidence, Medicines for Malaria Venture (MMV) joined forces with relevant stakeholders and partners to discuss the challenges relating to the treatment of severe malaria. The goal was to agree on a way forward to save more lives through increasing uptake and use of injectable artesunate across the malaria-endemic world. Representing 30% of the global population at risk, Nigeria and the Democratic Republic of the Congo (DRC) were identified as the two countries where the biggest impact could be made.

In July 2012, working with the National Malaria Control Programme (NMCP), key stakeholders and Clinton Health Access Initiative (CHAI), MMV set out to support six Nigerian states to make the switch. This involved raising awareness about the benefits of injectable artesunate, supporting a change to national guidelines, training healthcare workers, quantifying the need and monitoring the impact of the switch. Today, the drug is being procured with state funds in four of the six states.

In early 2013, the Programme National de Lutte Contre le Paludisme (PNLP) of the DRC adapted their policy with a new recommendation to use injectable artesunate as the preferred treatment for severe malaria. Making the switch, however, is a complex undertaking involving many operational and clinical adaptations. The strategic planning of the PNLP predicts that the percentage of patients present with severe malaria who receive injectable artesunate will increase from 30% in 2014 to almost all in 2016.

Based on the knowledge acquired in the DRC and Nigeria, MMV has established a severe malaria consortium with CHAI and the Malaria Consortium. In 2013, this MMV-led team was awarded a UNITAID grant of USD34 million to fund procurement and scale-up of injectable artesunate across 13 of the 36 states in Nigeria, and in five other high-burden African countries (Cameroon, Ethiopia, Kenya, Malawi and Uganda).

Up to 30-40 million vials of injectable artesunate would be needed worldwide each year to treat all estimated cases of severe malaria. Yet, currently, only 10 million vials are being manufactured annually. Owing to this shortfall and other constraints, an estimated 60-70% of severe malaria patients are left without access to the drug. The UNITAID project seeks to reduce this gap by stimulating greater market competition and eventually lowering prices for this important drug.

Focusing on safety

Following reports of haemolytic anaemia after treatment with injectable artesunate, in 2013, MMV convened a meeting to discuss the medicine's safety profile and make recommendations for its use.[5] Two key recommendations were made. First, physicians should be made aware of the need for continued monitoring of patients up to 28 days after treatment due to the possibility of delayed haemolysis after injectable artesunate administration. Second, further clinical trials need to be conducted in different patient populations to define the frequency and prognostic factors of haemolysis, and how to reduce them.

Later that year, WHO published a note building on these recommendations and concluding that there is overwhelming evidence that injectable artesunate is a generally well-tolerated and life-saving therapy, providing a significant reduction in mortality compared to quinine. The benefits of the medicine far outweigh the risks.[6]

To guide the optimal use of injectable artesunate as the scale-up proceeds, MMV is working with manufacturers to monitor the real-life safety of the medicine. For example, Guilin Pharmaceutical, who manufacture WHO prequalified injectable artesunate, has strengthened its pharmacovigilance activities to better assess the safety/tolerability of injectable artesunate in malaria-endemic countries.

> Since WHO prequalification in 2010, close to 12 million vials of Guilin's injectable artesunate have been delivered and are estimated to have saved between 80 000-90 000 additional lives compared to treatment with quinine.

Gathering evidence to support the switch

To gather the evidence to support the switch in the DRC and better understand the operational challenges, MMV, Swiss TPH and Kinshasa School of Public Health undertook the Malaria Treatment with Injectable Artesunate Study (MATIAS), which compared injectable

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artesunate treatment with quinine in four districts in and around Kinshasa.

The study consisted of two phases conducted sequentially at eight treatment centres, three hospitals and five health centres. In the first phase, 399 patients were recruited over a three-month baseline period and treated with intravenous quinine. Intravenous artesunate was then introduced for a following three-month period and 350 patients were treated. Consenting patients (if children via their parents) of two months of age or older with confirmed malaria were recruited. Four components were evaluated in each phase: 1) clinical assessment; 2) time and motion study;[7] 3) feasibility and acceptability assessment; 4) analysis of the financial costs.

Additionally, following reports of haemolytic anaemia after injectable artesunate administration, the protocol was adapted to include outcome and follow-up at days 14, 21, 28 after treatment, in addition to the already planned visit at day seven. The proportion of patients with severe anaemia in the study groups was below 1% for the whole duration of the follow-up period. In all cases, delayed anaemia was clinically manageable with appropriate and prompt care.[8] It should be noted that other studies have reported rates of delayed haemolysis in up to 7% of children treated with injectable artesunate.[9]

Overall, the respective case fatalities were 3.8% with quinine and 1.7% with artesunate, with a median time to discharge of three versus two days, respectively. The mean cost for treatment was 19-36 USD for quinine versus 17-28 USD for artesunate. Also, 75% of healthcare workers reported that artesunate was easier to use than quinine. The study therefore supports WHO recommendations for use of life-saving injectable artesunate for the treatment of severe malaria.[10]

The study findings provide compelling evidence about the feasibility of and positive health impact from introducing injectable artesunate in DRC, supporting its national deployment over three years through its inclusion into the country's 2013-2015 strategic plan.

Buying time for treatment

The first point of care for many patients with severe malaria is a community-level healthcare worker (CHW) or primary care facility. It is often not possible to deliver parenteral treatments at this level, and in such cases the WHO recommends the use of rectal artesunate suppositories (RAS)[11] as pre-referral treatment.

Thus, a WHO-prequalified RAS product is urgently needed to make treatment for severe disease available at this first point of care. This will buy time for them to seek services from higher-level (and better-resourced) health facilities with the capacity to provide the recommended treatment.

The aforementioned UNITAID grant is also being used to address this therapeutic gap. This process will build on clinical studies led by the WHO Special Programme for Research and Training in Tropical Diseases (WHO-TDR), which demonstrated the benefits of rectal artesunate.[12] MMV will support selected manufacturers of RAS to demonstrate bioequivalence between their products and the product used in WHO-TDR's studies, and subsequently seek WHO prequalification. Two such pharmaceutical partners have been identified and MMV is working with them to bring prequalified RAS to market by 2016.

In support of RAS rollout, MMV is conducting market research in 20 high-burden malaria countries to help optimise the use of the drug. The first step is to understand current guidance and practice regarding pre-referral treatment for severe malaria in priority countries. The next step will be to quantify the demand for rectal artesunate for 2016-2018 by the end of 2014 to help ensure that manufacturers can meet the need.

Conclusion

Today, we have a key tool to help save lives from severe malaria, injectable artesunate for treatment, and another one on the way, rectal artesunate for pre-referral treatment. MMV is working with partners to maximise the use of both. Already, tens of thousands of additional lives have been saved thanks to countries and healthcare workers making the switch from quinine to artesunate for treatment. Findings from the MATHIAS study have also demonstrated the feasibility of a switch. We know the impact this medicine can have and we know healthcare workers prefer to use it in place of quinine. Now is the time to work towards ensuring all severe malaria patients will receive this life-saving treatment. MMV will continue to work with partners to achieve this goal.

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The significance of community engagement in strengthening health systems

The Ebola epidemic has highlighted the importance of bridging trust and building common goals between the health profession and the communities they serve. Douglas Orr reports

The worst outbreak of Ebola ever seen is currently occupying headlines across the globe. As of 9 August, 1848 cases and 1013 deaths had been reported by the World Health Organization (WHO)[1] with health systems in Guinea, Sierra Leone and Liberia struggling to cope. In an editorial in June, The Lancet noted the key reasons why the new strain of the Zaire Ebola subtype was proving difficult to control: tracing infections across three countries with constant movements of people across porous borders is difficult; the countries already have weak health systems – compounded by the fact that health workers had never before dealt with Ebola; and finally, but perhaps most importantly, a lack of community trust in government has greatly hampered the response effort. The extent of this distrust was evidenced in Sierra Leone's Kailahun district, where Ebola was initially seen by communities as a government conspiracy to depopulate the area. The stoning of health workers was the result.[2]

Prior to the current outbreak of Ebola, the largest outbreak had been in Uganda in 2000. Francis Omaswa was then Director General of Health Services in Uganda and oversaw the efforts to control that outbreak. Writing in August in the Lancet Global Health Blog, he emphasised the importance of community engagement in tackling the epidemic: 'The single most important lesson we learned was that building and holding public trust by the government and health personnel is the foundation for all control efforts'.[3] Intensive communication with communities, supported by engagement with the media and local leaders working alongside community health workers (village health teams), and the introduction of field technology for quick field diagnosis were seen as key to the response. Mr Omaswa highlighted the importance of strong primary healthcare principles: leadership, good governance, and 'active participation of the people themselves'. He cautioned that these principles should be institutionalised, because they are needed anyway, and because there will be future Ebola outbreaks. The primary healthcare principles that Omaswa refers to were laid out in the Alma Ata Declaration of 1978, described by WHO as the 'major milestone of the twentieth century in the field of public health'.[4] Article 4 of the Declaration enshrines the importance

of community engagement in healthcare: 'The people have the right and duty to participate individually and collectively in the planning and implementation of their healthcare.' A systematic review conducted in 2011 noted that 'community engagement and participation has played a critical role in successful communicable disease control and elimination campaigns in many countries.'[5] Examples cited in the review included the elimination of malaria in Taiwan, of schistosomiasis in Guanxi Province in China, of malaria in Aneityum, Vanuatu, and of onchocerciasis in 2002 in 11 West African Countries.

Community engagement means different things in different contexts. It covers a range of terms such as 'community participation', 'community involvement', 'community empowerment', 'community based'.[6] Only by adding the question 'for what?' to the end of each of these terms do we get closer to understanding what motivations inform a specific intervention and what the term might look like in practice: 'community participation for what?' The 'spectrum of community engagement' proposed by the International Association for Public Participation provides useful clarification. It consists of five stages along a continuum of increasing community impact: inform, consult, involve, collaborate, empower. At the inform end of the spectrum, information is provided to the public, while at the empower end, final decision-making is taken at the community level. In between, communities might be consulted to obtain feedback, involved in developing options and collaborate in implementing solutions.

In the lessons learnt from the management of Ebola in the Uganda case, we can see that elements of the first four stages were seen to be necessary. As we progress from one stage to the next, the distance between the community and the official diminishes. Decisions

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become less remote and are increasingly within the purview of the community. As the distance reduces, clarity emerges about the necessity of interventions. Misinformation can be better managed. Community concerns can then be more quickly recognised and addressed. To what extent this actually happens and how responsive officials are, is fundamental to creating and sustaining community trust. It is a gradual and ongoing process to enable the success of interventions. If community trust in the system does not already exist to some extent, then interventions flounder, as can be seen in some areas of the current Ebola response.

So, how can we foster community engagement in health systems beyond the informing and consulting stages of the engagement spectrum? Healthcare committees are one mechanism for bringing together health workers and community representatives to plan, implement and monitor health services, and activities in many countries in Africa. But if they are to be effective, a number of factors need to be in place. Research conducted by Equinet in several African countries has resulted in a number of recommendations. To increase the effectiveness of healthcare committees, the following are essential:

a. Healthcare committees need to be backed up by enabling national public health laws and policies. Without them, the committees may not be recognised by health managers nor able to receive funds.
b. Such enabling laws and policies should themselves be supported by constitutional rights to health, to healthcare, and to public participation and information.
c. Governments should establish by regulation the roles, composition, powers, duties, capacities of and resources for healthcare committees, including to:
    - Facilitate health literacy and public health information;
    - Facilitate community identification of health needs and priorities and bring this evidence to health services;
    - Ensure community voice in health systems, with attention to disadvantaged groups;
    - Prioritise, plan and budget services with health personnel;
    - Engage stakeholders and communities on resourcing and implementing health plans;
    - Monitor health expenditures, services and actions and their impact;
    - Ensure accountability of services to the community;
    - Provide feedback to and review progress with communities;
    - Report and engage on the progress, challenges and needs of community and primary care levels at higher levels.
d. Healthcare committees should be democratically elected.
e. Healthcare committees' capacity to fulfil their roles should be built in an ongoing way, with resources provided within health budgets for both the capacity building and functioning of the committees.
f. Tools and guidance to enable the monitoring and accountability of the performance and impact of healthcare committees and health services ('social accountability tools') should be established.

At Crown Agents, we have had to work extensively on building community empowerment into the South Sudan Health Pooled Fund, as was stipulated as one of the primary objectives of the whole project. We are fund manager of the three-year, multi-donor programme, which is aimed at delivering and strengthening health services in six out of South Sudan's ten states. We had learned from previous funding mechanisms that community engagement and participation, when done in an ad hoc fashion, had achieved inconsistent degrees of success, and that interventions and innovations from Non-Governmental Organisations had not been fully documented. As a result, we established a Community Strategy Advisor role, who specifically led work to engage with the community and Ministry of Health perspectives, as well as with cross-cutting stakeholders. The Community Strategy Advisor has worked with community-based organisations, community healthcare committees, the fund's staff, and with individuals told draft, implement and maintain a comprehensive Community Strategic Plan. The plan to support and build the vital links would allow the people of South Sudan to assist with the building of their own healthcare provisions.

It is vital not to underestimate the importance of law and policy in helping to create an enabling environment for community engagement and, by extension, the effective delivery of and access to services and therefore, health outcomes. The recent AIDS2014 conference held in July in Melbourne, Australia highlighted the importance of this, particularly in relation to Key Affected Populations – those most vulnerable and likely to be exposed to HIV, including men who have sex with men, people who inject drugs, sex workers and transgender people. Speaking at the conference, Lord Fowler, former UK Health Secretary under Margaret Thatcher noted: 'Thirty-five million have HIV - half have not been diagnosed. One of the reasons for that is obviously the prejudice and ostracism that comes with either being gay, or having HIV, or being a sex worker. It's such a hostile environment to come forward. If you're going to be prosecuted, it's most unlikely you'd want to come forward to say: 'please test me I think I may have HIV'."[7] It is therefore imperative to establish robust political and regulatory environments in which community interventions can flourish, built on foundations of trust, collaboration, and cooperation between the community and health services.

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Superficial fungal infections

Roderick Hay

Abstract

Superficial fungal infections or mycoses are common treatable conditions seen in everyday clinical practice, although they may also present differently in immunosuppressed patients. The dermatophyte or ringworm infections, superficial candidiasis of the mouth, skin or genital tract and infections due to *Malassezia*, such as pityriasis versicolor, are the main conditions. Although they present with typical clinical changes, generally diagnosis is enhanced by direct microscopy or culture of suitable samples. Treatment largely depends on the use of azole (imidazole/triazole) or allylamine antifungals, applied in short courses topically or for longer periods orally, depending on the site and severity of the infection.

Keywords dermatophytosis; fungal infections; *Malassezia* infection; superficial candidiasis; superficial mycoses

Superficial fungal infections include common skin diseases, and rare infections confined to specific geographical areas or groups of patients.[1–3] But together they are the fourth commonest cause of human disease and the commonest infection.[4]

The principal diseases are:

- dermatophytosis (ringworm – tinea capitis, tinea pedis)
- superficial candidiasis (cutaneous, oropharyngeal, vaginal)
- disease caused by *Malassezia* spp. (pityriasis versicolor, seborrhoeic dermatitis).

Dermatophytosis

Dermatophyte fungi are organisms that digest keratin. They belong to three principal genera – *Trichophyton*, *Microsporum* and *Epidermophyton*. They are also grouped according to their natural habitat: geophilic (soil), zoophilic (animals) and anthropophilic (humans). Transmission is indirect through desquamated epidermis or hairs, or direct through bodily contact.[3]

Dermatophytosis is an infection of the skin and the keratinized structures (hair, nails) arising from it. In the skin, the archetypal lesion is annular with central healing (ringworm or tinea). Clinical descriptions are based on the site of infection. Tinea pedis is estimated to affect up to 15% of the healthy population,[5] and fungal nail disease (onychomycosis, see *MEDICINE* 2013; **41:** 382–386) more than 15% depending on age.

- Dermatophyte lesions may scale and itch. In tinea corporis, the lesion may be annular.
- In tinea pedis, skin erosions or blisters develop in the web spaces, and the soles may be covered with dry scales.
- Lesions of tinea cruris in the groin have a prominent rim.
- Tinea capitis (scalp ringworm, Figure 1 and Figure 2) is a disease of childhood presenting with alopecia and scaling on the scalp. The incidence of this infection has increased in the UK, Europe and the USA because of the spread of anthropophilic species,[6,7] particularly *Trichophyton tonsurans*.
- In untreated AIDS patients, dermatophytosis may lead to widespread or atypical infections and rapidly spreading white onychomycosis involving the whole nail plate.

Dermatophytosis is often confused with other common skin conditions that also form rings (e.g. eczema, annular erythemas, granuloma annulare). Tinea capitis may also be difficult to recognize, because the hair loss is often patchy and confined to small areas or single hairs. The diagnosis of dermatophytosis should be confirmed in the laboratory.

Superficial candidiasis

Superficial *Candida* infections are usually caused by *Candida albicans*. This organism is a common commensal in the mouth, vagina and gastrointestinal tract in healthy individuals. The prevalence of carriage is greater in hospitalized patients and in those with conditions that predispose to candidiasis.

Oropharyngeal candidiasis (oral thrush) the typical symptoms and signs are soreness and white patches on an erythematous background (plaque type).[8] An erythematous variety, often seen in HIV-positive patients, exists; it does not have plaques, but sore areas of erythema are typical. Acute or chronic infection may occur in the immunocompromised. Other predisposing factors include antibiotic therapy and dentures.

Vaginal candidiasis (vaginal thrush) is a common infection, the clinical appearances of which are similar to those of oropharyngeal disease, plus discharge. Pruritus may also occur, and recurrent episodes are common. Women with vaginal thrush seldom have underlying predisposing factors.

Candidiasis of the skin is often confined to body folds, including the interdigital spaces of the hands or feet. Typically, small satellite pustules lie distal to the periphery of the rim of the rash. Chronic paronychia (nail-fold infections) may be caused by *Candida* (Figure 3).

Malassezia infection

Malassezia spp. are common surface commensals of greasy skin (e.g. scalp, chest). They are associated with pityriasis versicolor, seborrhoeic dermatitis and folliculitis. *Malassezia* infection may complicate chronic central venous cannulation, mainly in neonates, manifesting as pulmonary infiltrates on chest radiography.

Pityriasis versicolor is a scaly, hypo- or hyperpigmented rash on the trunk (Figure 4). It is common in tropical regions and in patients who have recently taken a holiday in a hot climate. The patches may resemble vitiligo, but the presence of scaling is typical.

Seborrhoeic dermatitis is a common scaly condition affecting the face (including the nasolabial folds), the front of the chest and the scalp (dandruff).[9] Severe seborrhoeic dermatitis is particularly common in patients with AIDS or chronic neurological conditions such as Parkinson's disease.

Malassezia folliculitis is an itchy, follicular rash on the upper back and shoulders that may resemble acne.

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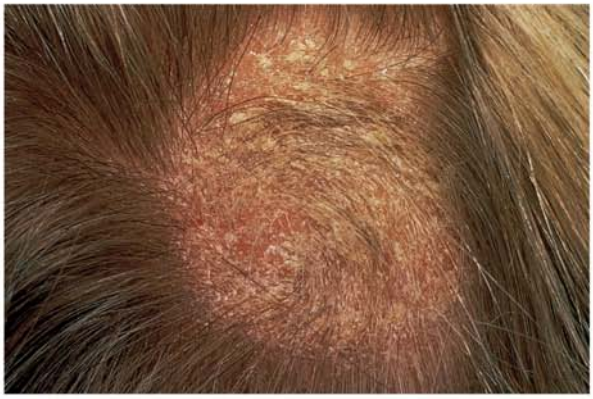

Figure 1 Inflammatory tinea capitis caused by *Microsporum canis* acquired from a cat.

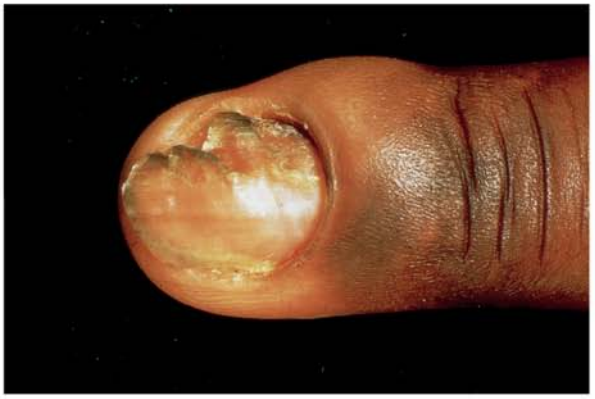

Figure 3 Chronic *Candida paronychia*. In this patient, the infection is centred on the nail-fold.

Laboratory diagnosis

The key to diagnosis is the demonstration of the organisms in skin scales, hair or nails. Scrapings are taken with a scalpel or nail clippers. They are examined in potassium hydroxide or a fluorescent stain such as *Calcofluor*, and can be cultured on Sabouraud's medium. Skin scales, hair and nails can be sent to a laboratory folded in a card (transport packs are available). Material from mucosal surfaces is best sent on a moistened swab. Routine molecular diagnostic measures are not available.

Management

See Table 1. Topical antifungals (e.g. terbinafine, imidazoles such as clotrimazole) are necessary in most circumscribed infections. The duration of treatment is 1–4 weeks. Nail infections require systemic treatment with terbinafine, 250 mg daily for 6–12 weeks or itraconazole, 400 mg daily for 1 week every month for 3 months.[10]

- Tinea capitis is treated with griseofulvin, terbinafine or itraconazole. Clinical trials suggest that terbinafine, at conventional dosage, is more effective in *Trichophyton* infections, griseofulvin or itraconazole in *Microsporum* infections.
- Treatment of *Candida* infections in immunocompetent patients involves topical azoles or polyene antifungals (e.g. nystatin, amphotericin). Oral fluconazole or itraconazole may be necessary in more severe infections and in infections in immunocompromised patients, but there are

Figure 2 Tinea capitis caused by an anthropophilic fungus (*Trichophyton tonsurans*). Signs such as scaling can be minimal.

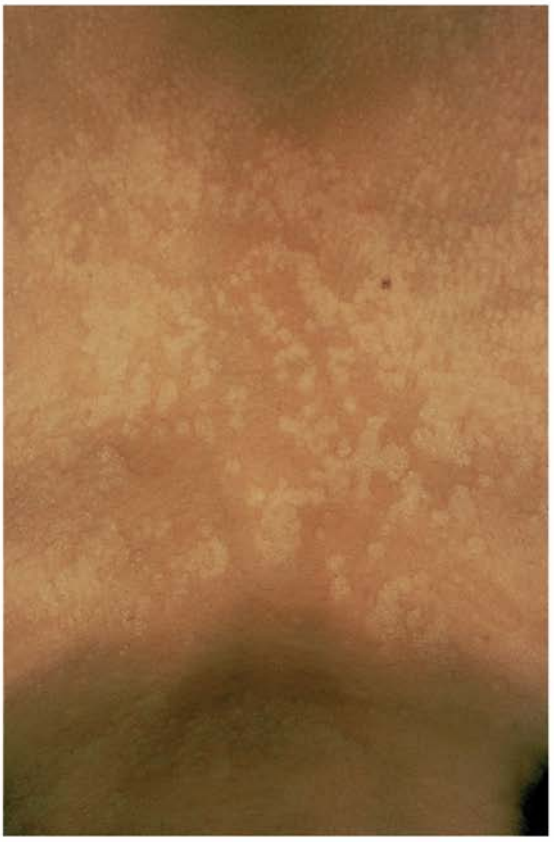

Figure 4 Pityriasis versicolor caused by *Malassezia*. Scaling may be difficult to see in such cases.

Antifungal therapy

Antifungal	Site of action
Topical treatments for all superficial mycoses*	Cell membrane — 14α demethylase
• Imidazoles (cream, ointment, powder) (e.g. clotrimazole, miconazole, econazole, ketoconazole)	
• Allylamine antifungals (e.g. terbinafine)	Cell membrane — squalene epoxidase
Oral treatments	Cell membrane — 14α demethylase
• Triazoles (itraconazole, fluconazole) — all superficial mycoses	
• Terbinafine — dermatophytosis	Cell membrane — squalene epoxidase
• Griseofulvin — dermatophytosis (tinea capitis)	Inhibition of mitotic spindle formation
*Topical polyenes (e.g. nystatin, amphotericin) are sometimes used for oral or vaginal infections in non-immunocompromised patients	Cell membrane — binds to ergosterol causing cell membrane leakage

Table 1

important interactions with other drugs such as ciclosporin and rifampicin. Resistance to fluconazole is a recognized problem, particularly in infections caused by *Candida krusei* or *Candida glabrata* and long-term suppressive treatment with this drug should be avoided if possible.

- The usual treatment for pityriasis versicolor is a topical azole or terbinafine. In extensive infections, itraconazole, 200 mg/day for 5 days, may be used. ◆

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Tuberculous meningitis

Guy Thwaites

Abstract

Tuberculous meningitis (TBM) is caused by *Mycobacterium tuberculosis* and kills or disables around a half of sufferers. It is commonest in young children and those infected with HIV, but can affect all age-groups. TBM presents with non-specific symptoms over days or weeks, followed by worsening headaches, fever, and vomiting. Without anti-tuberculosis chemotherapy, cranial nerve palsies (typically VIth and IIIrd nerves) and hemiplegia may develop, and consciousness becomes impaired. Mortality exceeds 50% if the Glasgow Coma Scale score is less than 10/15 by the time the patient starts treatment. Early diagnosis and treatment improves outcome but is notoriously difficult as current laboratory tests lack sensitivity. Early empirical therapy is often required to improve the chance of survival. Rifampicin-based anti-tuberculosis chemotherapy should be used whenever possible and given for 9–12 months. Adjunctive corticosteroids are recommended for all patients with TBM for the first 6–8 weeks of treatment, regardless of age, disease severity, or HIV infection. Hydrocephalus, cerebral infarction, and expanding tuberculoma are common complications of TBM, occurring at any time before or after treatment starts. Brain imaging, preferably with MRI, is recommended to assess the evolution and management of these complications. Ventriculo-peritoneal shunting should be considered in those with hydrocephalus and falling consciousness.

Keywords diagnosis; management; treatment; tuberculous meningitis

Introduction

TBM represents around 1% of all forms of tuberculosis, but with more than 8 million tuberculosis cases worldwide each year, and successful vaccination programmes against other causes of meningitis (e.g. *Neisseria meningitidis*), *Mycobacterium tuberculosis* is now the commonest cause of bacterial meningitis in many settings. In the UK there are approximately 200 TBM cases reported annually, which is similar to the numbers of meningococcal meningitis cases reported.

Epidemiology

TBM is commonest in young children and those infected with HIV. In populations with high tuberculosis prevalence the peak age of TBM incidence is from 0 to 4 years. In populations with lower tuberculosis prevalence, most cases of TBM are in adult immigrants from areas of high tuberculosis prevalence. Other risk factors for TBM include alcoholism, diabetes mellitus, malignancy, recent corticosteroid use and treatment with tumour necrosis factor-α (TNF-α) inhibitors.

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Pathology

TBM results from the haematogenous dissemination of *M. tuberculosis* from the lung.[1] Blood-borne bacteria travel to the brain where they can settle and initiate a localized granulomatous inflammatory response called a 'Rich focus' (after the early 19th century pathologist, Arnold Rich). TBM develops when a Rich focus comes into communication with the subarachnoid space, releasing *M. tuberculosis* into the cerebrospinal fluid (CSF). Classically, the basal meninges are affected, with inflammatory exudates in the basal cisterns obstructing normal CSF flow and causing hydrocephalus.[2] Localized necrotizing granulomatous inflammation can lead to tuberculoma formation (ring-enhancing space-occupying lesions) and vasculitis with stroke syndromes. The perforating arteries of the middle cerebral artery are most commonly affected, leading to basal ganglia and internal capsule infarcts.

Clinical features

The clinical features of TBM are non-specific and, as summarized in Figure 1, progress to death if not treated.[3] The most important differential diagnoses are partially treated pyogenic bacterial meningitis and cryptococcal meningitis.

The onset of symptoms is usually insidious: young children may come irritable, feed poorly, and lose weight, whilst adults feel fatigued, lose their appetite and may suffer night sweats. These prodromal symptoms can last from a few days to several weeks, before more pronounced meningitic symptoms are reported, with headache, fever and neck stiffness. If the patient is left untreated, confusion and coma follow over the ensuing days, and around 50% of sufferers will develop focal neurological deficit, either cranial nerve palsies (VIth and IIIrd are the commonest) or hemiplegia.

CSF analysis is essential in the diagnosis of TBM and typically reveals 50–1000 white cells/mm,[3] with a mixture of neutrophils and lymphocytes. CSF protein is elevated, typically 1.5–5.0 g/litre, and the ratio of CSF:plasma glucose is less than 50% in more than 95% of patients.

Laboratory diagnosis

The performance of the commonly available laboratory diagnostic tests for TBM is summarized in Table 1. Nucleic acid amplification tests (e.g. polymerase chain reaction (PCR)) cannot be used to rule out the diagnosis.[4] The inadequacies of all currently available diagnostic tests mean that empirical treatment, without microbiological confirmation, is often required.

Other investigations

Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain can demonstrate the typical pathological features of TBM, and imaging of other organs (e.g. lungs, liver, spleen) may assist in the diagnosis of tuberculosis. The commonest brain imaging features of TBM are hydrocephalus and basal contrast-enhancing exudates; both features are more common in children (~80%) than adults (~40%) and may be absent in the elderly or immunosuppressed with TBM.[5]

The natural history of untreatedtuberculous meningitis

Time (weeks)		0	1	2	3	4	5	
Clinical	Fatigue	+	++	++	++	++	++	DEATH
	Fever	+/−	+	+	+	+	+	
	Headache	+/−	+	++	++	++	++	
	Consciousness			↓	↓↓	↓↓↓	↓↓↓	
	Focal signs			+	++	++	++	
	MRC grade	I	I	II	II/III	III	III	
Cerebrospinal fluid	White cells		↑ Neutrophils	↑ Neutrophils	↑	↑	↑	
	Protein	↑	↑	↑↑	↑↑	↑↑	↑↑	
	Glucose		↓	↓	↓↓	↓↓	↓↓↓	
	Lactate		↑	↑	↑↑	↑↑	↑↑↑	
	Bacteria		+	+	+	++	++	
Brain imaging	Hydrocephalus		+	++	+++	+++	+++	
	Infarction			+	++	++	++	
	Tuberculoma				+	+	++	
Mortality		5%	10%	20%	30%	50%	80%	
Time (weeks)		0	1	2	3	4	5	

MRC, Medical Research Council.

Figure 1

Drug treatment

The principles of successful TBM treatment are:[6]

- anti-tuberculosis treatment must be started early, before the onset of coma, to give the best chance of disability-free survival
- isoniazid and rifampicin are the key components of the treatment regimen and should be used whenever possible
- interruption of therapy during the first 2 months of treatment is an independent risk factor for death
- prolonged therapy (9–12 months) is required to prevent disease relapse.

The currently recommended treatment regimens for children and adults are the same as for all other forms of tuberculosis, except that the continuation phase of treatment should be extended to at

Summary of the performance of laboratory tests performed on cerebrospinal fluid (CSF) for the diagnosis of tuberculous meningitis (TBM)

Test	Sensitivity	Specificity	Comment
Ziehl–Neelsen stain	10–60%	98–100%	Sensitivity substantially improved by meticulous microscopy of large volumes of CSF (>8 ml)
Mycobacterial culture	40–60%	100%	Takes 3–8 weeks: too slow to aid clinical decision-making, but essential for drug susceptibility testing
Nucleic acid amplification (e.g. PCR)	40–60%	95–100%	Good 'rule in' test, but should never be used to 'rule out' the diagnosis of TBM
Adenosine deaminase activity	60–90%	80–90%	Performance varies according to the assay and cut-off used. Specificity main problem: cannot differentiate pyogenic bacterial meningitis from TBM. Not recommended as routine test
Interferon-γ release assay (e.g. T-spot.TB)	50–70%	70–90%	Performance varies according to cut-off (spots or interferon-γ concentration) and requires substantial volume of CSF (and cell numbers) to work. Not recommended as routine test

Table 1

least 7 months (9–12 months' total treatment).[6] The merits of adjunctive corticosteroid treatment of TBM have been debated for 50 years. A recent Cochrane systematic review and meta-analysis of seven randomized controlled trials, involving 1140 participants, concluded that corticosteroids reduced death and disability in HIV-negative children and adults with TBM, but the benefit in HIV-infected individuals remains uncertain.[7] The effect on survival was consistent across all grades of disease severity. Current UK guidelines recommend adults (>14 years) should start treatment with dexamethasone 0.4 mg/kg/24 hours with a reducing course over 6–8 weeks. Children should be given prednisolone 4 mg/kg/24 hours (or dexamethasone 0.6 mg/kg/24 hours) for 4 weeks, followed by a reducing course over 4 weeks.[6]

Management of complications

Hydrocephalus, infarction and expanding tuberculoma are common complications of TBM.[8] Communicating hydrocephalus can be managed initially with diuretics (furosemide and acetazolamide), although ventriculo-peritoneal shunting may be required if the patient's conscious level falls. Shunting is nearly always required for those with coma and non-communicating hydrocephalus.

Tuberculomas develop in nearly all patients after the start of therapy and the majority are clinically silent. Sometimes, tuberculomas cause significant clinical problems by enlarging or coalescing, and liquefying to cause an abscess. Corticosteroids may reduce tuberculoma size and help control symptoms. Other anti-inflammatory agents, such as thalidomide, have been used when corticosteroids fail to help. Occasionally, large abscesses require aspiration or excision.

Cerebral infarction occurs in around 30% of patients, usually within the first 8 weeks of therapy. There is limited evidence to suggest that aspirin (150 mg/day) may reduce the risk of TBM-associated cerebral infarction.[9]

Prognosis

TBM prognosis depends upon the severity of disease at presentation, conventionally defined by the modified Medical Research Council (MRC) grades I–III. Patients with Grade I TBM (Glasgow Coma Scale (GCS) score 15/15 and no focal neurological deficit) have around a 90% chance of disability-free survival. Patients with Grade II TBM (GCS 10–14, or GCS 15 with focal neurological deficit) have around a 75% chance of disability-free survival. Patients with Grade III TBM (GCS <10) have a less than 50% chance of surviving without long-term disability.

Prevention

TBM can be prevented by reducing *M. tuberculosis* transmission and by *Bacillus* Calmette–Guérin (BCG) vaccination. The former depends on the rapid identification and treatment of adults with infectious pulmonary tuberculosis, and the follow-up and treatment of newly infected contacts. The latter depends on targeted BCG vaccination of neonates. ◆

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Practice points

- Strongly consider tuberculous meningitis (TBM) in all patients with meningitis and more than 5 days of symptoms
- If TBM suspected, take a large volume of cerebrospinal fluid (>8 ml) for Ziehl–Neelsen stain and mycobacterial culture
- Never rule out TBM on the basis of negative microbiological/molecular tests; treat early and empirically if TBM strongly suspected
- UK guidelines currently recommend four drugs (rifampicin, isoniazid, pyrazinamide, ethambutol) for 2 months, followed by 10 months of rifampicin and isoniazid for the treatment of TBM
- Adjunctive dexamethasone should be given to all patients with TBM, regardless of disease severity
- Hydrocephalus is the commonest serious complication of TBM and an external ventricular drain/shunt should be considered if associated with falling consciousness
- TBM is prevented through assiduous community control of tuberculosis and *Bacillus* Calmette–Guérin vaccination of neonates

(See page 56)

Part one

Part two/three

Part four

Q1 (b) (c) (d) Ingrid's history, her relatively good health and the lack of clinical findings on examination tend to suggest that this is a dietary problem rather than a serious life-threatening illness. However, lack of neurological symptoms and signs does not rule out pernicious anaemia, B12 or folate deficiency. Peripheral nerve symptoms often arise late in such deficiencies.

Q2 (d) Dietary deficiency must be the initial diagnosis until proven otherwise. Students are often unaware of how badly they are feeding themselves!

Q3 (b) Given her history and the blood picture (a red cell volume of 112fL is well above the norm of 85-101) of macrocytic anaemia, the first priority is to give together the two vitamins deficiency of which is most likely to cause it. It is important to give oral iron as well to prevent depletion of iron stores. After treatment you should monitor serum potassium levels and the reticulocyte response. There should be no need for transfusion. Only if there is no response to the vitamin treatment should malabsorption tests (or delving into drug use) be considered.

Q4 (a) (b) (c) (d) (e) (f) (g) All of these can cause macrocytic anaemia, but most are only considered if there are a relevant history and examination findings. In Ingrid's case, investigations into these possible causes were unnecessary, as she responded almost instantaneously to her double vitamin treatment. She was advised how to eat more appropriately, and is now enjoying a normal life, feeling fit and healthy, with fruit and vegetables on her daily menu.

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

Medicine Review

Outcome of XDR tuberculosis

No African health workers need to be reminded of what a major problem tuberculosis (TB) is. Globally it is now estimated that at least 5% of cases are multidrug-resistant (MDR), and of these about 5-10% are extensively drug-resistant (XDR). The figures are probably higher in Africa, and certainly are in South Africa. Here, 10% of TB cases in 2008 were MDR, and in 2011 there were 500 confirmed cases of XDR-TB. Currently it is estimated that South Africa has the highest number of XDR cases in the world. XDR is generally defined as MDR disease, with resistance to a fluroquinolone, and either amikacin, capreomycin or kanamycin. An important report has recently been published by a South African group of researchers with extensive experience of XTR-TB. This concerns the long-term outcome of the condition, and results are of considerable concern.[1]

A total of 107 patients with microbiologically confirmed XDR-TB were enrolled between March 2008 and August 2012. Of these, 44 (41%) were HIV positive, and 64% of isolated bacteria were resistant to at least eight drugs. The patients were treated as in-patients for prolonged periods of time, with a median of eight separate drugs. At two years follow-up 49 (46%) had died, and at 5 years the mortality was 78 (73%). Default rates were 7% and 4% at two and five years respectively; and treatment failure rates were 23% and 10%. Mortality was not related to HIV status.

These gloomy figures show the seriousness of XDR-TB. With a near 80% five year mortality, the outcome is worse than most malignant conditions. Also, significant numbers of sputum-positive patients (defaulters or treatment failures) are re-entering the community, and therefore likely to spread the disease.[2] The South African researchers describe the current status of XDR-TB as 'an acute global health crisis', and it is hard to argue with their viewpoint. Urgent and adequately funded research is needed to discover and trial new drugs to treat this fearsome new menace.

Not so neglected NTDs?

A recent Lancet editorial reviews progress in tackling what are now widely known as 'Neglected Tropical Diseases' (NTDs).[3] These conditions include African and South American trypanosomiasis, filariasis, schistosomiasis, trachoma, onchocerciasis, soil-transmitted helminthiasis, leishmaniasis, leprosy and dracunculiasis. A major meeting of NTD stakeholders in London in 2012 made a declaration ('The 2012 London Declaration') to control or eradicate these major 10 NTDs by 2020. In April 2014, a further meeting (this time held in Paris) was convened to review progress in achieving the London Declaration aims.

There has certainly been impressive progress. In 2013 there were an estimated 1.35 billion treatments given for these 10 diseases, a 35% increase since 2011 Drug donations have increased – these were given to 37 countries in 2011 and 55 in 2012. Over 70 countries now have national NTD programmes. Drug company involvement in research and treatment supply has increased, and several academic NTD departments now exist.

This is excellent news. NTDs are clearly no longer 'neglected' in the usual sense of the word. Nevertheless, there is still much work to be done. It is estimated that still only 36% of patients in need of NTD drugs receive them. There seems to be a particular problem with anti-schistosomal drugs, as in 2012 only 31 of 52 countries with endemic schistosomiasis had treatment programmes. Political and social unrest is a problem in some areas - for example the African Horn, Afghanistan and Pakistan - and this can seriously interfere with drug supply. Political will and adequate finances are also continuing problems.

The fight for the 2020 goals must still therefore go on. NTD specialists must also consider how 'control' of the 10 major NTDs is to be defined, as it seems certain that most will not be eradicated by 2020.

Clostridium difficile in Africa

The bacteria Clostridium difficile is a major problem in western countries. It causes a troublesome diarrhoeal disease, often associated with preceding antibiotic use. It was first recognised as 'pseudo-membranous colitis', and was particularly associated with clindamycin therapy; though now the true bacterial cause is known, and it is recognised that a wide variety of antibiotics can act as precipitants. C.difficile diarrhoea can be highly infectious on hospital wards, and in the UK, patients are all cubicle nursed, and usually treated with oral metronidazole. The disease particularly affects the old and debilitated, and can sometimes be fatal, or at least contribute to death.

Up to now there has been little information on C.difficile prevalence in Africa, but a recent study from Zimbabwe has given useful new information.[4] A total of 268 diarrhoeal stool samples from various clinics and hospitals in Harare were cultured, and 23 (8.6%) were positive for C.difficile. The age range of the affected individuals was interesting - 12 were 2 to 10 years old, four were 21 to 30 years old, two were 31 to 40 years old, three were 51 to 60 years old, and two were over 60 years.

Unfortunately no information was available on recent antibiotic usage, or other co-morbidities (in particular HIV/AIDS infection). Nevertheless, if nearly 10% of diarrhoea in sub-Saharan Africa is potentially due to C.difficile, then adequate testing for this organism is vital, with appropriate therapy and measures to stop cross-infection.

Raising awareness of acute HIV infection

The illness of acute HIV-1 infection has been well recognised for many years. Sometimes called 'seroconversion syndrome', it occurs about two weeks after viral transmission. It is characterised by fever, myalgia, headache and sometimes rash. At this stage the patient is highly infectious. Not surprisingly, acute HIV infection may closely resemble an attack of malaria, but new work from East Africa shows that the diagnosis is often not considered.[5,6] The research showed that HIV testing was only done in 16% of young (18-29 years) adults presenting with fever. Yet acute HIV infection is probably as common as malaria in this age range.

The authors of the report point out that guidelines for investigating and treating fever in sub-Saharan Africa tend to concentrate too much on malaria. HIV testing should be considered in all young adults presenting with fever, especially if they are sexually active and the malarial slide is negative. Anti-retroviral therapy at this stage would not only improve patient outcome, but would also reduce HIV transmission in general.

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STIs Review

Syndromic management

Sexually transmitted infections (STIs) continue to be a significant health burden, especially in low- and middle-income countries. The World Health Organization (WHO) estimates that almost half a billion cases of curable STIs (gonorrhoea, chlamydia, syphilis, trichomoniasis) occur every year, a number virtually unchanged in the past decade.[1] In addition, at least 536 million people are infected with incurable herpes simplex virus, and an estimated 291 million women have human papillomavirus (HPV) infection at any point in time. There are many cost-effective tools for prevention and treatment of STIs, but their application in resource limited settings has been inadequate. Syndromic management has long been the go-to diagnostic tool in the absence of laboratory services. This clinical approach can be very effective for assessing urethral discharge, but is notoriously poor when applied to other syndromes, such as vaginal discharge, and fails to identify asymptomatic infections. An assessment of syndromic management of STIs as part of the Kisumu Incidence Cohort Study found syndromic management to be insufficient.[2] The Kisumu study was an observational prospective cohort study to estimate the incidence of HIV seroconversion. Many studies of syndromic management take place within STI clinics, where clients have already self-selected for STI diagnosis and treatment. This study took place within a research context, where all participants were asked about STI signs and symptoms, and assessed how well syndromic and laboratory aetiological diagnoses matched. In this group, syndromic management missed the majority of STI infections. Overall, 10.8% of participants were diagnosed with an STI through syndromic management, while 32.2% had an STI confirmed with laboratory testing. Herpes simplex virus type 2 was the most prevalent STI. The study also compared responses of participants to clinician-administered computer-based personal interviews with participant self-administered computer-based interviews. Participants were more likely to report symptoms of STIs in the self-administered interviews, a finding that might improve syndromic management in some situations. Another study in Kisumu compared self-reporting of STI symptoms with clinician-initiated questions.[3] HIV-infected women attending an HIV clinic were asked if they had any current health complaints. After their routine visit, the women were interviewed specifically about abnormal vaginal discharge and received a speculum exam. The study found that the 13 women who self-reported STI-related symptoms in their routine visit did not have laboratory-confirmed disease (testing for N. gonorrhoeae, C. trachomatis and T. vaginalis). Of the 41 women who tested positive for an STI, 78% (32/41) reported no symptoms at all and 31% (10/32) would have been diagnosed with an STI-based on clinical exam. This study indicates that having clinicians ask women about any vaginal complaints, and/or a speculum examination can significantly improve diagnosis of STIs in this population.

Vaccines

There are more than 30 bacterial, viral and parasitic pathogens classified as STIs. Many of these infections can be cured, but antibiotic resistance, especially against N. gonorrhoeae, is a growing problem. There are currently only two STI vaccines, against hepatitis B and human papillomavirus. There is now renewed interest in pushing forward the development of new STI vaccines. In 2010, the Decade of Vaccines was initiated, and in 2012, the 194 member states of the WHO approved a Global Vaccine Action Plan. This plan is a roadmap for stakeholders, such as governments, health professionals, academics, manufacturers, global agencies, civil society, the media, and the private sector, to follow in improving immunisation worldwide.[4]

In April 2013, the WHO convened a technical consultation on STI vaccines. These experts focused on the development of new vaccines against five STIs: HSV-2, chlamydia, gonorrhoea, trichomoniasis and syphilis. Participants discussed the current knowledge base and status of vaccines, critical knowledge gaps, and next steps for accelerating vaccine development and availability. A special issue of the journal Vaccine, co-edited by the WHO and the U.S. National Institute of Allergy and Infectious Diseases, captures much of the technical information discussed at the consultation and is an excellent resource.[5] While the obstacles are many,

there is reason to be hopeful that vaccines can make an impact on STI morbidity and mortality. Experience with the hepatitis B and HPV vaccines demonstrates that with investment in science, a thorough analysis of the public health need and potential global markets, and with strong political leadership, STI vaccines can have an impact.[6,7]

HPV, cervical cancer and genital warts

It was not until 1992 that scientists discovered that HPV was the cause of cervical cancer. More than 100 HPV types have been identified, and it is now known that HPV types 16 and 18 are associated with 70% of invasive cervical cancers. The highest incidence of cervical cancer is in sub-Saharan Africa, and the disease is the most common cause of cancer deaths among women in the region. HPV types 6 and 11 are responsible for 90% of genital warts (condyloma acuminata). While considered benign, genital warts can be difficult to treat and often recur.

The prevalence of HPV among women with normal cervical cytology is an average of 24% in sub-Saharan Africa, higher than rates found in more developed countries.[8] The highest incidences of HPV infection and cervical cancer are found in Eastern and Western Africa. HIV infection increases the incidence and prevalence of all HPV-related diseases. Given the aging of the population, concomitant HIV infections and lack of preventive services, the already significant incidence and mortality due to HPV is expected to grow over the next two decades in Africa.

There are now two effective vaccines that can protect against certain HPV types. The bivalent vaccine, Cervarix™, protects against types 16 and 18. The quadrivalent vaccine, Gardisil™, protects against types 6, 11, 16 and 18. Both are given in a three-dose schedule over six months and are very effective. Studies show that among women who have not been infected with HPV prior to vaccination, the quadrivalent vaccine is nearly 100% protective again genital warts caused by types 6 and 11, and 83% effective against all genital warts.[9]

Following the establishment of national HPV vaccine programmes in Australia, Sweden, Denmark and the US, the number of genital wart cases in these countries has fallen. Australia began vaccinating women aged 12-27 years in 2007. In 2008, the proportion of women under age 28 with genital warts declined by 25%.[8] Five years later, there were no warts diagnosed in vaccinated women, and warts were rare among men and women under age 21, suggesting that the reproductive rate of the virus had fallen below one. Such a rapid response is largely due to the high vaccination coverage rate in Australia (over 70%), and the data shows what a significant and swift impact HPV vaccination can have within a population.

Effective HPV vaccination programmes depend on vaccinating those at risk prior to infection with HPV. This means fully vaccinating young girls ages 9-13 before the initiation of any sexual activity which could infect them with HPV. To help make this a reality in many parts of the world, the Global Alliance for Vaccines and Immunisations (GAVI) has negotiated a reduced price of US$4.50/dose for the HPV quadrivalent vaccine (it costs up to US$120/dose in more developed countries), and has begun pilot HPV vaccination programmes in many countries.[10] By December 2013, 20 countries had qualified for GAVI assistance in introducing HPV vaccine programmes in Africa, and demonstration projects have begun in Kenya, Ghana, Madagascar, Malawi, Niger Sierra Leone and Tanzania.

A modelling study of the cost-effectiveness of HPV vaccination found that vaccination of 58 million 12-year-old girls in the 179 countries studied would prevent 690 000 cases of cervical cancer and 420 000 deaths, mostly in low- and middle-income countries, at a cost of US$4 billion.[11] The authors conclude that HPV vaccination is cost-effective in 87% of the countries studied and is very cost effective in low-income countries with the highest vaccine-preventable burden of cervical cancer, but these countries also are least likely to have country-level HPV vaccine programmes.

Most vaccination campaigns focus on young girls because they are most at risk from HPV infection, and it is thought to be most cost effective. If vaccination coverage among young girls is over 50%, it is expected that the entire population will experience herd immunity. While the overall burden of HPV-associated disease is highest among women, recent studies highlight that HPV infection is also common in men and boys. HPV infection in men is associated with anal, oropharyngeal and penile cancers. A systematic review and meta-analysis of HPV infection in men in sub-Saharan Africa found a pooled prevalence of any HPV was 78.2% among HIV-positive men, and 49.4% among HIV-negative men.[12] A study of HPV types found in cancerous and pre-cancerous penile lesions among men in South Africa found a high variety of HPV types.[13] Of the 51 samples analysed, HPV types 11 and 16 had similar incidences. In pre-cancerous lesions, HPV 11 was most frequent (80%), followed by HPV 31 and 16 (25% each) and several other types. In cancerous lesions, HPV 16 was most common (62.9%), followed by HPV 11 (34.3%), and several others. Several lesions showed from two to six HPV types in one lesion. These results indicate that young boys in South Africa, who may be exposed to many HPV types as young as age 10, could benefit from vaccination.

Research continues on HPV vaccines, and a nine-valent vaccine which covers types 6, 11, 16, 18, 31, 33, 45, 52, and 58 is in clinical trials. The effectiveness of using two doses of the current vaccines instead of three is also being examined. Despite the challenges of logistics and cost, it is clear that high coverage HPV vaccination programmes can have a significant impact on health and are worth the investment.

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Paediatrics Review

Vitamin D deficiency and rickets – a worldwide disorder

Rickets, generally considered a disease of toddlers, can have long-term effects, including obstructed labour and reduced bone size and mass in adulthood.[1] Vitamin D deficiency (VDD) during peak periods of growth, e.g. term infants, the first two years (6-24 months) of life and puberty, is the main cause of rickets and VDD during pregnancy is an important factor in the early manifestation in infants. There is no clear threshold of vitamin D (VD) level below, which rickets will develop as the level of calcium intake is also important.[1] In Nigerian children exposed to adequate sunlight, hypocalcaemia is the major factor in the cause of rickets.[2,3] However, in African children where dietary calcium levels are low, a higher level of VD may be required to maintain normal bone metabolism.[4] A recent case control study of 67 Indian children with nutrition rickets and 68 age, and sex-matched healthy controls found significantly lower levels of calcium and higher dietary phytate levels in ricketic infants, but no significant difference in the 25 hydroxy vitamin D (25OHD) levels between the two groups.[5] In children with borderline low 25OHD, the dietary calcium level may be crucial in the development of rickets and both are important in treatment. Thus, rickets exists along a spectrum between isolated VDD to isolated calcium deficiency, with perhaps other environmental and in some cases genetic factors also involved.[2]

Aetiology

Vitamin D_2 (ergocalciferol), obtained from the diet or vitamin D_3 (cholecalciferol), the form synthesised in skin and found in cod liver oil are hydroxylated to 25OHD (calcidiol) in the liver.[1] This is excreted by the proximal renal tubules where it undergoes 1-hydroxylation to 1,25dihydro vitamin D ($1,25(OH)_2D$) (Calcitriol). Its main function is increasing calcium absorption from the gut. Failure to absorb calcium stimulates release of parathyroid hormone, which results in loss of phosphate by the kidneys. Absence of phosphate at the growth plate and failure of mineralisation of osteoid results in rickets. However, in rickets of prematurity which usually occurs in infants born before 28 weeks the cause is deficiency of phosphate and other minerals rather than VDD.

VDD in term infants in the first few weeks of life is due to maternal VDD and commonly presents with hypocalcaemic convulsions. Rarely it presents as cardiomyopthy. In the period 2000-2006, 16 infants (three weeks - eight months old) were admitted to paediatric cardiac units in south east England with cardiomyopathy associated with hypocalcaemia and low VD levels; six had cardiac arrest and two died.[6] All were from ethnic minorities and all had been breast fed. Similar cases have been reported from India.[7]

Maternal 25OHD crosses the placenta and undergoes placental conversion to $1,25(OH)_2D$ and at birth 25OHD concentration in cord blood closely correlates with maternal levels.[8] Unless the mother is on a near pharmacological dose of VD, e.g. 100µg per day (4000 IU. 1µg =40 IU) breast milk will contain very low levels of VD (<1.5 µg/L).[1] The daily requirement for young infants is 10 µg/day. Infants born to replete mothers who are exclusively breast fed will be VDD after eight weeks.[8]

There is negligible VD synthesis during winter months at latitudes greater than 35° in the northern hemisphere and the 32° latitude in the southern hemisphere.[4] Increased concentration of melanin in the skin reduces the ability of ultraviolet B (290-315 nm range) to convert 7-dehydrocholesterol to previtamin D.[1] Thus, dark skinned people require more prolonged sunlight exposure than those light skinned to obtain equivalent amounts VD. Recommended sunshine exposure in the UK for white children and adults is 15 minutes of unshaded noon-time exposure, three times per week, with 35% skin surface exposed. However, studies using simulated sunlight exposure have demonstrated that South Asian adults in the UK require more than threefold longer exposure to produce comparative amounts of 25OHD to white adults.[9] In the Middle East and other Islamic regions, where cultural and religious customs dictate the type of clothing for women and adolescent girls, the entire body may be covered apart from the face and hands. Throughout the world the youth of today now spend much of their time outside school hours indoors watching television or working with computers.

Decreased atmospheric pollution in industrialised countries since the 1950s due to clean-air legislation is likely to be one of the factors in the decrease in incidence of VDD at least in the white skinned population. There is some evidence that the increase in air pollution in large urban conurbations in low- and middle-income countries is also a factor in the increased incidence of VDD, such as in India[10] and elsewhere.

In high-income countries the increased incidence of rickets is mainly in recent immigrants with pigmented skin.[1]

Genetic disorders such as vitamin D receptor (VDR) gene polymorphism may also be a factor in the aetiology of rickets in Asians, especially Chinese populations.[11]

Definitions of vitamin D deficiency

Measurement of VD is difficult and complex, and thus is unlikely to be available in many non-research laboratories in low-income countries. Also, there is no clear agreement on cut-off levels for defining deficiency. A vitamin level required for optimal growth may differ from that required to prevent rickets.[1] The following are commonly used definitions: severe deficiency < 27.5 nmol/L; deficiency 27.5-50 nmol/L; and insufficiency 50-75nmol/L.

The incidence and prevalence of rickets is difficult to estimate and rates will change with socioeconomic development. The more studies of 25OHD undertaken in the childhood population the more likely will be the finding of subclinical and pre-rackitic VDD.[12] The geographical distribution of rickets has been recently reviewed.[2,13]

Prevention

Prevention of rickets comprises public awareness and public health efforts to promote the importance of adequate sun exposure and VD intake through diet and supplementation. However, in societies where children and adolescent women are not exposed to adequate sunshine for cultural reasons, the former alone is unlikely to succeed. Also, in some western countries because of concerns about skin cancer, excessive restriction of sun exposure and use of high factor sun cream may reduce endogenous production of VD.

Presently, regimens for VD supplementation in high-income countries are principally aimed at people living in high latitudes in northern Europe and Canada, and immigrants with skin pigmentation. However, regimens and doses differ between countries.

The UK Department of Health advice is as follows:[1] All pregnant and breastfeeding women should receive daily supplements of VD. However, the usefulness and safety of VD supplementation during pregnancy is not established in rigorous randomised trials.[14] If the mother is not taking supplements throughout pregnancy, her infant may need to commence VD drops from one month of age. Otherwise the infant should start supplementation at six months and continue until five years of age. Pre-term infants are at particular risk. Most formula milk, breakfast cereals and margarines are fortified with VD. In the UK, fortification of chapatti flour aimed at the Asian community is effective in raising VD levels, but is not universally used.[1]

In low- and middle-income countries, where VD supplementation of foods are not routine, each region needs to establish a practical regimen for VD supplementation depending on variables such as latitude, cultural attitudes regarding exposure to sun light, women's clothing and socioeconomic status. In countries where poor children have inadequate VD intake, dietary calcium supplementation may also be necessary.[5] Advice regarding eating VD-rich foods (fish liver oils, fatty fish, mushrooms, egg yolks and liver) is unlikely to succeed in poor societies.

In Turkey, where VDD rickets was endemic, especially in the eastern part, nationwide free VD supplementation was effective in virtually eradicating rickets.[15]

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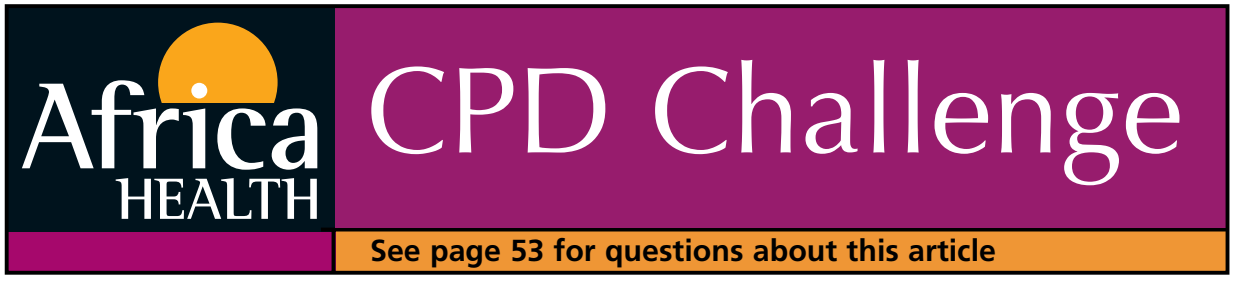

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Oncology

Mammography screening for breast cancer

Ten years ago, a review by the World Health Organization (WHO) estimated mammography screening may reduce breast cancer mortality by around 25%. However, advances in treatment has now led experts to question the value of screening.

A Norwegian prospective study investigated the effectiveness of contemporary mammography screening on breast cancer mortality among women aged 50-79 years. The authors analysed the mortality rates of women invited to screening during implementation of the programme in comparison to those not invited.

During 15,193,034 person-years of observation, 1175 women died from breast cancer in the invited group compared with 8996 who were not invited to screening. After adjustment for confounding factors the mortality rate associated with being invited to mammography screening ratio was calculated at 0.72. To prevent one death, it was estimated that a total of 368 women would need to be invited to screening.

Invitation to modern mammography screening may reduce deaths from breast cancer by around 28%.

Weedon-Fekjaer H, Romundstad P, Vatten J. Modern mammography screening and breast cancer mortality: population study. *BMJ.* 2014; 348:3701.

Adjuvant exemestane in premenopausal breast cancer

Adjuvant therapy with an aromatase inhibitor improves outcomes, as compared with tamoxifen in post-menopausal women with hormone-receptor positive early breast cancer. A recent study investigated whether disease-free survival was greater among women receiving ovarian suppression, together with either tamoxifen (n=2358) or the aromatase inhibitor, exemestane (n=2359).

Although overall survival did not differ between the two groups, disease-free survival at five years was greater in the exemestane group (91.1%), compared with tamoxifen group (87.3%), yielding a significant hazard ratio (HR) of 0.72. The rate of freedom from breast cancer at five years was also significantly greater in the exemestane group (92.8% versus 88.8%). The rate of adverse events were similar between the two groups.

Ovarian suppression with exemestane compared with tamoxifen reduces the risk of recurrence.

Pagani O, Regan M, Walley B, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *NEJM.* 2014; 371:107–18.

Sorafenib treatment for thyroid cancer

Differentiated thyroid cancer can be effectively managed by surgical intervention, radioactive iodine administration, or L-thyroxine therapy. However, many patients with locally advanced or metastatic differentiated thyroid cancers become refractory to radioactive iodine. These patients have a poor prognosis due to a lack of efficacious treatment options.

A recent placebo-controlled trial investigated the effect of sorafenib, an oral kinase inhibitor, on progression-free survival amongst 417 with patients radioactive iodine-refractory thyroid cancer. Median progression-free survival was significantly longer in the sorafenib group (10.8 months) compared with 5.8 months in the placebo group (significant HR, 0.59). This was true for all clinical and genetic biomarker subgroups, irrespective of mutation status. Adverse events occurred in 204 of the 207 patients receiving sorafenib, with the most common being hand-foot skin reaction, diarrhoea, alopecia, and rash or desquamation.

Sorafenib significantly improved progression-free survival in patients with locally advanced or metastatic differentiated thyroid cancers.

Brose M, Nutting C, Jarzab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet.* 2014; 384:319–28.

Rheumatology

Stem cell transplantation for diffuse systemic sclerosis

Systemic sclerosis is an autoimmune connective tissue disease characterised by vasculopathy, autoantibody formation, and fibrosis. Management commonly involves cyclophosphamide, but new research has indicated that autologous haematopoietic stem cell transplant (HSCT) may be a viable alternative therapy.

A recent multicentre trial randomised patients with early diffuse cutaneous systemic sclerosis to receive either HSCT (n=79), or 12 successive monthly intravenous pulses of cyclophosphamide (n=77). The primary endpoint measured event-free survival (defined as death, or persistent major organ failure).

During a median follow up of 5.8 years, 22 events occurred in the HSCT group (19 deaths) and 31 in the cyclophosphamide group (23 deaths). During the first year, more events were recorded in the HSCT group compared with the control group, however, in the long term HSCT exhibited a significantly greater long-term event-free survival benefit (four year HR, 0.29).

Despite an increased treatment related mortality in the first year, HSCT conferred a long-term event-free survival benefit.

Van Laar J, Farge D, Sont J, et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. *JAMA.* 2014; 311:2490–8

Hydroxychloroquine for primary Sjögren syndrome

Primary Sjögren syndrome is a systemic autoimmune condition characterised by mouth and eye dryness, pain, and fatigue. Hydroxychloroquine is the most commonly prescribed immunosuppressant for the syndrome, despite limited evidence supporting its efficacy.

To investigate its efficacy, a three year trial consisting of 120 patients were randomly assigned 1:1 to receive either hydroxychloroquine (400 mg/d) or a placebo for a duration of 24 weeks. The primary endpoint measured the number of patients reporting 30% or greater reduction in scores on two out of three numeric scales measuring dryness, pain, and fatigue.

At 24 weeks, 17.9% of patients in the hydroxychloroquine group reached the primary endpoint compared with 17.2% in the placebo – an insignificant difference. Two serious adverse events were recorded by week 24 in the hydroxychloroquine group compared with three in the placebo group.

During the 24 week trial period, hydroxychloroquine did not improve symptoms.

Gottenberg J, Ravaud P, Puéchal X, et al. Effects of hydroxychloroquine on symptomatic improvement in primary Sjögren syndrome: the JOQUER randomised clinical trial. *JAMA.* 2014; 312:249–58.

Tofacitinib for rheumatoid arthritis

Methotrexate is currently the first-line treatment for rheumatoid arthritis, but there are considerable concerns about its safety and side effect profile. A recent trial assessed the efficacy of the biologic disease-modifying antirheumatic drug, tofacitinib (a JAK inhibitor), in comparison with methotrexate for patients with active rheumatoid arthritis.

A total of 958 patients were assigned to receive either 5mg or 10mg of tofacitinib or methotrexate over 10 weeks. Two scoring systems measuring structural joint damage (Sharp score) and the proportion of patients that had an ACR score ≥70 (measuring joint pain and swelling) were used as endpoints.

The primary endpoint was achieved in significantly more patients in both doses of tofacitinib compared with the methotrexate group. However, herpes zoster infections were more common in the tofacitinib group (4.0% vs 1.1%) as were confirmed cases of cancer (5 vs 1).

Tofacitinib is superior to methotrexate at reducing signs and symptoms of rheumatoid arthritis, but concerns exist over its safety and side effects.

Lee E, Fleischmann R, Hall S, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. *NEJM.* 2014; 370:2377–86.

Musculoskeletal

Epidural glucocorticoid injections for spinal stenosis

Lumbar spinal stenosis is caused by narrowing of the spinal canal resulting nerve root compression and in turn, pain, paraesthesia, and weakness. Glucocorticoid injections are widely used to treat the disability, despite limited evidence for its effectiveness and safety.

A North American randomised trial evaluated the effect of either glucocorticoid plus lignocaine injections or lignocaine injections alone. All 400 patients received either one or two epidural injections before the primary outcome was evaluated. It measured the score changes on a disability questionnaire (higher scores indicate greater physical disability).

At six weeks, although scores in both groups had reduced, there were no significant between-group differences in the disability scores. Further, no significant differences were found according to type of injection (interlaminar vs. transforaminal).

Epidural injections of glucocorticoids, plus lignocaine offered no minimal or short-term benefit as compared with lignocaine alone.

Friedly J, Comstock B, Turner J, et al. A randomised trial of epidural glucocorticoid injections for spinal stenosis. *NEJM.* 2014; 371:11–21.

Anaesthesia during hip fracture surgery

Hip fractures are serious injuries that carries as significant risk of mortality and morbidity with 4-10% of patients dying within 30 days of hospital admission. It has been hypothesised that anaesthesia type may influence mortality rate, therefore, a recent retrospective cohort analysis investigated the in-hospital all-cause mortality among patients receiving different types of anaesthesia. A total of 73 284 patients undergoing hip fracture surgery were investigated, of which 84% underwent general anaesthetic, 9.5% recieved regional anaesthesia, whilst 6.5% had combined anaesthesia.

In-hospital deaths occurred in 2.2% of patients undergoing general anaesthesia, 2.1% and 2.4% of those patients receiving regional and combined anaesthesia, respectively. Further analysis calculated the risk for regional anaesthesia was 0.91 when compared with general anaesthesia, and 0.98 for combined.

Hip fracture surgery mortality did not significantly differ between anaesthesia types.

Patorno E, Neuman M, Schneeweiss S, et al. Comparative safety of anesthetic type for hip fracture surgery in adults: retrospective cohort study. *BMJ.* 2014; 348:4022.

Treatment for intra-articular fractures of the calcaneus

Many calcaneal fractures are severe high-energy fractures and often result in prolonged recovery and poor outcomes. To date, there is no consensus as to whether operative management involving open reduction and internal fixation provides better outcomes than the non-operative management utilising splints, elevation, ice application, and early mobilisation.

A recent randomised trial compared the pain and function scores in patients receiving either operative or conservative management post-injury. A total of 151 patients with closed, displaced, intra-articular calcaneal fractures were randomised in a 1:1 ratio between the two groups. Results showed that although pain and function had improved in both groups by 24 months, no significant difference was noted between the two groups. However, both complication and reoperation rates were higher in the operative care group (odds ratio (OR), 7.5).

No symptomatic or functional advantage was observed after surgical management of calcaneal intra-articular fractures of the calcaneus.

Griffin D, Parsons N, Shaw E, et al. Operative versus non-operative treatment for closed, displaced, intra-articular fractures of the calcaneus: randomised controlled trial. *BMJ.* 2014; 349:4483.

Obs & Gyn

The effect of gravity on placental transfusion volume

Delayed cord clamping allows for the passage of blood from the placenta to the baby, and reduces the risk of iron deficiency in infancy. Recommendations advise holding the infant at the level of the vagina for one minute to allow gravity to increase the transfusion volume. However, this process can interfere with the immediate contact of the infant with the mother and may cause low compliance.

A randomised trial assessed the effect of gravity on the placental transfusion volume by comparing the difference in weight before and after cord clamping between those babies held at the level of the vagina (introitus group) versus those held to the mother's chest (abdomen group) during the two minutes following birth. Primary analysis included 197 babies in the introitus group and 194 in the abdomen group. The mean weight gain in the introitus group was 56g versus 53g in the abdomen group - a non-significant difference.

The position of the baby before cord clamping does not affect the placental transfusion volume.

Vain N, Satragno D, Gorenstein A, et al. Effect of gravity on volume of placental transfusion: a multicentre, randomised, non-inferiority trial. *Lancet.* 2014; 384:235–40.

Preconception aspirin and pregnancy

Pregnancy loss is estimated to occur in up to 30% of conceptions. However, some studies have indicated that administration of low-dose aspirin post-conception may positively affect pregnancy outcomes, but there is limited evidence supporting this. Yet the effect of preconception use of low-dose aspirin for pregnancy outcomes has not yet been assessed.

A multicentre trial recruited 1228 women (aged 18-40) with a history of pregnancy loss. They were then randomised to receive either 81mg of aspirin daily or a placebo, in addition to folic acid for up to six menstrual cycles or 36 weeks gestation. The primary outcome assessed the livebirth rate.

Of the 535 women in the aspirin group, 58% had livebirths compared with 53% in the placebo group, which resulted in a non-significant difference in livebirth rate of 5.09%. Both adverse events and pregnancy loss rate did not differ between the two groups.

Preconception low-dose aspirin is

not recommended for the prevention of pregnancy loss.
Schisterman E, Silver R, Lesher L, et al. Preconception low-dose aspirin and pregnancy outcomes: results from the EAGeR randomised trial. *Lancet.* 2014; 384:29–36.

Interpregnancy interval and birth outcomes

The time interval between pregnancies is considered an important and modifiable risk factor for adverse birth outcomes. Typically, short intervals (<18 months between birth and conception), and long intervals (>23 months) have a higher risk of preterm birth, small for gestational age birth, and low birth weight. However, much of the previous research does not adjust for confounding factors such as genetic predispositions, and socioeconomic status.
A recent retrospective cohort study examined the effect of interpregnancy intervals on the incidence of adverse pregnancy outcomes among 40 441 mothers. The study also adjusted for maternal confounding factors.

After adjustment for confounding factors, the risk involved with short interpregnancy intervals were more modest than previously estimated. The adjusted OR for short interpregnancy intervals (0-5months) was 1.07 for preterm birth, 1.03 for low birth weight, and 1.08 for small for gestational age. However, adjusted OR still showed a persistent high risk of small for gestational age and low birth-weight for long interpregnancy intervals.
Ball S, Pereira G, Jacoby P, et al. Re-evaluation of link between interpregnancy interval and adverse birth outcomes: retrospective cohort study matching two intervals per mother. *BMJ.* 2014; 349:4333.

Letrozole for infertility in polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility. Current first-line treatment for infertility among these women involves treatment cycles of clomiphene; however, it has poor efficacy and a relatively high multiple pregnancy rate. Aromatase inhibitors, including letrozole, may provide better outcomes.

To compare the two treatments a randomised trial assigned women to receive either letrozole (n=374) or clomiphene (n=376) for up to five treatment cycles. The primary outcome measured live-births during the treatment period.

Women receiving letrozole had significantly more cumulative live-births than those receiving clomiphene (25.5% vs. 19.1%; rate ratio for live-birth, 1.44) without any significant differences in overall congenital abnormalities. Cumulative ovulations was also significantly higher in the letrozole group than with clomiphene (61.7% vs. 48.3%). No significant inter-group differences were observed for pregnancy loss or twin pregnancy.

Higher live-birth rates were achieved with letrozole compared with clomiphene.
Legro R, Brzyski R, Diamond M, et al. Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome. *NEJM.* 2014; 371:119–29.

CPD Challenge

See page 53 to test yourself on this article

Pain Management

Telecare for management of chronic pain

Chronic musculoskeletal pain is the most common symptom reported in primary care. Despite this, few clinical trials investigating interventions enhancing pain management have been published, or the optimisation of analgesic therapy.

The SCOPE randomised trial assessed the effectiveness of a telecare intervention for chronic pain versus usual care in 250 patients with chronic musculoskeletal pain. The intervention group received 12 months of telecare management, coupling an automated symptom monitoring with, and algorithm-guided approach to optimising analgesic.
The usual care group received all care from their primary care physicians. The primary outcome measured self-reported pain scores (0-10; higher scores signify more pain).

Pain scores showed a significant one point reduction in pain score in the telecare group compared with the usual care group. Patients in the intervention group were also more likely to show >30% improvement in pain scores.

Telecare management increased the proportion of patients with improved chronic musculoskeletal pain.
Kroenke, K, Krebs, E, Wu, J, and Yu Z. Telecare collaborative management of chronic pain in primary care: A randomised clinical trial. *JAMA.* 2014; 312:240–8.

Naloxegol for opioid-induced constipation

Between 40% - 90% of patients taking opioids suffer from constipation or other debilitating gastrointestinal side effects. Recently, a new drug, naloxegol (an oral, peripherally acting μ-opioid receptor antagonist) has been assessed for its efficacy against opioid-induced constipation in two identical randomised trials.

A total of 1352 were assigned to receive either a daily dose of 12.5 or 25mg of naloxegel or placebo. The primary outcome measured the 12-week response rate, which was defined as ≥3 spontaneous bowel movements per week and an increase of ≥1 spontaneous movements over the trial period.

Response rates were significantly higher with 25mg of naloxegol than with placebo (intention to treat population: 44% versus 29%; and in patients who had an inadequate response to laxatives: 49% versus 29%). Response rates were also significantly higher than placebo for those patients receiving 12.5mg of naloxegol.

Naloxegol resulted in a reduction of opioid-induced constipation without reducing the analgesic effects.
Chey W, Webster L, Sostek M, et al. Naloxegol for opioid-induced constipation in patients with noncancer pain. *NEJM.* 2014; 370:2387–96.

HIV/AIDS

Dolutegravir for HIV-1 infection

Boosted protease inhibitor regimens are often preferred as first-line therapy for treatment-naïve patients with HIV/AIDS. However, dolutegravir is an integrase inhibitor that can be taken once daily without pharmacokinetic boosters, and boasts a reduced profile for drug interactions. A recent non-inferiority trial assessed the efficacy of dolutegravir versus a guideline-recommended boosted protease inhibitor-based regimen.

A total of 484 treatment-naïve patients were randomised to receive either dolutegravir 50mg once daily or darunavir 800mg plus ritonavir 100mg once daily. The primary endpoint was the proportion of patients with HIV-1 RNA concentration lower than 50 copies per mL by week 48.

After 48 weeks, 90% of the patients receiving dolutegravir has reached the primary endpoint versus 83% in the darunavir-ritonavir group. Analysis revealed that dolutegravir is not only non-inferior, but also superior to darunavir-ritonavir treatment. No treatment-emergent resistance was recorded, but two patients in each group had confirmed virological failure.

Once-daily dolutegravir is superior to once daily darunavir plus ritonavir.
Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO):

48 week results from the randomised open-label phase 3b study. *Lancet.* 2014;383:2222–31.

Antiretroviral therapy initiation after HIV self-testing

Achieving a high coverage of HIV testing is a major challenge, but self-testing can overcome some barriers to conventional facility- or community-based testing. However, no research has investigated the initiation of HIV care after self-testing. In the present study, the authors investigated whether offering optional home initiation of HIV care increases the demand for antiretroviral therapy (ART).

A total of 16 600 Malawian residents from 14 clusters nationwide received self-testing kit and were then allocated to facility-based, or optional home initiation of HIV care for those with positive results. The primary outcome measured proportion of adults initiating ART. After six months, a significantly greater proportion of those in the home group than in the facility group had initiated ART (2.2% vs 0.7%; risk ratio 2.94). Further, significantly more adults reported positive tests in the home group.

Offering home initiation of HIV care rather than standard care increases the proportion of adults initiating HIV care.

MacPherson P, Lalloo D, Webb E, et al. Effect of optional home initiation of HIV care following HIV self-testing on antiretroviral therapy initiation among adults in Malawi: A randomized clinical trial. *JAMA.* 2014; 312:372–9.

Implementations of HIV interventions

Epidemiological data shows substantial variation in the risk of HIV infections between communities within African countries. A recently paper hypothesised by focussing on interventions of key populations at high risk of HIV infections could improve the effect of investments in the HIV response.

Using Kenyan data, the authors investigated the potential gains in the efficiency and effectiveness of investments focussed on the people and places at highest risk, rather than a uniform, national approach.

Results established that a uniformly distributed combination of HIV prevention interventions could reduce the total number of new HIV infections by 40% during a 15-year period. With no additional spending, this effect could be increased by 14% during the 15 years - almost 100 000 extra infections, and result in 33% fewer new HIV infections occurring every year by the end of the period if the focused approach is used to tailor resource allocation to reflect patterns in local epidemiology.

The focused approach achieves greater effect than the uniform approach despite exactly the same investment.

Anderson S, Cherutich P, Kilonzo N, et al. Maximising the effect of combination HIV prevention through prioritisation of the people and places in greatest need: a modelling study. *Lancet.* 2014; 384:249–56.

Misc

Recombinant phenylalanine ammonia lyase for phenylketonuria

Phenylketonuria is an inherited disease caused by a deficiency of the enzyme phenylalanine hydroxylase. A recent trial assessed the safety and efficacy of phenylalanine ammonia lyase, an enzyme conjugated with polyethylene (rAvPAL-PEG) given to sufferers as a method of reducing phenylalanine concentrations which, when raised can cause neurocognitive dysfunction.

A total of 25 patients were randomised to receive subcutaneous injections of rAvPAL-PEG at escalating doses in order to assess the safety and tolerability of rAvPAL-PEG. The treatment was effective in all patients at the highest dose, reducing the phenylalanine concentration by over 50%. The lowest phenylalanine concentrations were observed six days post-injection, and were near-baseline by day 21. Adverse reactions included injection-site reactions and dizziness, while 60% of patients receiving a high rAvPAL-PEG dose developed generalised skin rashes.

Higher doses of rAvPAL-PEG reduce phenylalanine blood concentrations while remaining fairly safe and were well tolerated.

Longo N, Harding C, Burton B, et al. Single-dose, subcutaneous recombinant phenylalanine ammonia lyase conjugated with polyethylene glycol in adult patients with phenylketonuria: an open-label, multicentre, phase 1 dose-escalation trial. *Lancet.* 2014; 384:37–44.

Familial risk of cerebral palsy

Cerebral palsy is the most common cause of physical disability in children resulting from damage to the immature brain. However, the causes of the disability remain largely elusive, and whilst many studies have identified risk-factors during pregnancy and the perinatal period, few have investigated the heritable component of cerebral palsy.

A recent cohort study investigated the risks of recurrence of cerebral palsy in family members. Analysis of Norwegian national records estimated if one twin had cerebral palsy, the relative risk of recurrence was 15.6 in the other twin. In families with an affected singleton child, the risk was increased 9.2-fold in the subsequent full sibling, while affected parents were also at increased risk of having an affected child (6.5-fold). After exclusion of preterm births (a strong risk factor for cerebral palsy), familial risks remained and were often stronger.

People born into families in which someone already has cerebral palsy are themselves at elevated risk.

Tollanes M, Wilcox A, Lie R, et al. Familial risk of cerebral palsy: population based cohort study. *BMJ.* 2014; 349:4294.

New treatments for acute bacterial skin infections

Acute bacterial skin infections are a common cause of hospitalisation. Frequent causative pathogens for skin infections include *Staphylococcus aureus*, streptococci and methicillin-resistant Staphylococcus aureus (MRSA), which poses significant treatment challenges. Recently, two new antibiotic agents, oritavancin and dalbavancin, have been trialled to assess their efficacy and safety in treating acute bacterial skin infections.

Oritavancin, a lipoglycopeptide, has concentration-dependent activity with bactericidal activity against gram-positive bacteria, and a prolonged half-life that allows for single-dose treatment. The SOLO I trial compared the efficacy of a single intravenous dose of 1200mg of oritavancin, with a twice daily intravenous dose of vancomycin for 7-10 days. Analysis from 950 patients found only a 1.5% difference in efficacy between the treatments (oritvancin, 82.3% compared with 78.9% for vancomycin), and a similar frequency of adverse events. A single dose of oritavancin was non-inferior to a twice daily dose of vancomycin for gram-positive skin infections.

The second drug, dalbavancin, also a lipoglycopeptide agent was tested in the DISCOVER trials. It randomised patients to receive either intravenous dalbavancin on days one and eight of treatment or intravenous vancomycin (for at least three days) with the option to switch to oral linezolid treatment. The pooled analysis showed dalbavancin efficacy was non-inferior to the vancomycin-linezolid treatment (79.1% versus 79.8%, respectively). Fewer adverse events were reported in the dalbavancin group. Intravenous doses of dalbavancin on day one and eight was non-inferior to intravenous vancomycin alongside linezolid treatment.

Corey R, Kabler H, Mehra P, et al. Single-Dose Oritavancin in the Treatment of Acute Bacterial Skin Infections. *NEJM.* 2014; 370:2180–90.

Boucher H, Wilcox M, Talbot G, et al. Once-weekly dalbavancin versus daily conventional therapy for skin infection. *NEJM.* 2014; 370:2169–79.

Africa HEALTH CPD Challenge

Questions

Were you paying attention? Test your retentive capacities on issues raised in this edition of *Africa Health*. You can quietly test yourself, or – and we're particularly keen on this – you could make it a part or the foundation of a Journal Club in your department or health institution. Life-long learning is a collaborative exercise and the whole health team can be positively stimulated by being involved in such discussion.

Q1. Ebola coverage

i. From Francis Omaswa's informed opinion piece about dealing with the Ebola outbreak in Uganda in 2000, name two of the three key lessons that he describes as the key learning points from the episode.

ii. From Shima Ghoh's equally informed opinion piece, I was tempted to ask you to recount the scientific process used to produce the Zmapp…but that would be unfair (though I urge you to read it if you haven't). Instead: what is the means by which the Ebola virus attaches itself to human cells?

iii. Name three of four products that will eliminate the virus at appropriate concentrations?

iv. When faced with a possible Ebola patient what is the single most important measure you should take:
a. Always wear gloves
b. Use a disposable thermometer
c. Take time to get a full history from the patient

v. In setting up isolation areas, what space should you ensure separates out each of the beds? Should it be:
a. 1 meter
b. 3 meters
c. 5 meters

vi. Personal Protection Equipment (PPE) is vital for direct patient care of suspected or confirmed patients. Please list the different elements of protection available, and think about what you should use AT MINIMUM from arrival at your hospital gate, if your hospital is managing Ebola in its isolation unit.

vii. Soiled bed linen of patients with Ebola should be incinerated after use. Is this statement true or false?

viii. All medical waste (needles, syringes, tubing and other infectious waste) need to be carefully collected and buried in a designated pit of around 2m in depth. Should faeces, urine and vomit from the patient also be disposed off in this pit?

ix. If in caring for a patient you think you might have had contact with any body fluids or blood, what should you do?

Q2. Non Ebola questions

i. How many artemisinin combination therapies are now on WHOs recommended list?

ii. How many vials of injectable artesunate would be needed world wide to treat all cases of severe malaria?
a. Just under 10 million
b. Between 15 and 25 million
c. Between 30 and 40 million

Q3. Clinical Review: STIs

i. Syndromic management of STIs is the most accurate way to diagnose STIs in low resource settings. True or false?

ii. Are there any effective vaccines currently available to prevent STIs?

iii. Immunisation campaigns are expensive. Is it cost-effective to use HPV vaccines in sub-Saharan Africa?

Q4. Medicine Digest

i. Mammography screening has been under pressure in recent years with questions about its benefits. In a large scale Norwegian study, invitation to modern mammography screening produced results which:
a. confirmed this view
b. provided no significant new evidene
c. went against the recent evidence

ii. Name two of the three frequent causative pathogens for skin infections?

Africa HEALTH CPD Challenge

Answers

Q1.

i. a) the building and holding of public trust by the government and health personnel is the foundation for all control efforts.
b) recruitment of the support of community or village leaders working alongside the village health teams.
c) the introduction of new technology for quick field diagnosis of new infections.

ii. A glycoprotein.

iii. i) Heat; ii) alcohol-based products; iii) Sodium hypochlorite (bleach); and iv) calcium hypochlorite (bleaching powder)

iv. i) Always wear gloves…

v. i) Ensure at least 1 meter gap between beds

vi. PPE equipment includes: gloves, medical mask, goggles/face shield, an impermeable gown to cover clothing; closed, puncture resitant shoes (rubber boots); and possibly a waterproof apron for certain activities. If possible a stethoscope for each patient. In terms of what to wear where, best to refer you back to the second and third page of the guidelines as the answer is of course long!

vii. False. It needs to be handled with great care, but can be washed in the laundry, or (again with precautions) by hand in a drum. In exceptional circumstances it might be incinerated.

viii. No. Human waste and liquid waste from washing can be disposed of in the sanitary sewer or pit latrine. No further treatment is necessary.

ix. Stay calm. Immediately and safely stop any current task and leave the patient area. Remove PPE with great care, and then wash the affected site initially with soap and water (or eyewash solution if affecting the eye). Then report the incident to the local coordinator. You will then need to enter daily evaluation for 21 days before hopefully being cleared of suspicion.

Q2.

i. Five, with a sixth on the way.

ii. Between 30 and 40 million doses

Q3.

i. False. Syndromic management of STIs can be very effective for certain syndromes, such as urethral discharge, but is far less accurate for other syndromes, including vaginal discharge. Syndromic management also fails to identify asymptomatic disease. While laboratory confirmation of disease is the gold standard, many settings do not have access to such services, making syndromic management a vital, but limited tool.

ii. Yes. There are currently vaccines effective against hepatitis B and against the human papillomavirus (HPV). Research is underway to develop vaccines against other STIs, including HSV-2, chlamydia, gonorrhoea, trichomoniasis and syphilis.

iii. Yes. While immunisation campaigns can be costly, the effect of protecting against future disease is important. Experiences in more developed countries have found that HPV vaccination programmes that achieve good coverage have a significant and rapid effect on reducing the incidence of genital warts in the population. Modelling studies show HPV vaccination is cost-effective, especially in low-income countries with high burden of cervical cancer. The high cost of the HPV vaccines and the novelty of reaching young girls age 9-13 for immunisation are significant challenges. However, GAVI has negotiated reduced prices for HPV vaccines and is offering financial support for low income countries to establish HPV programmes.

Q4.

i. It revealed that modern screening may reduce deaths from breast cancer by around 28%

ii. The three are: Staphylococcus aureus, streptococci, and methicillin-resistant Staphylococcus aureaus (MRSA).

Teamwork and partnership

An update on activities from our **Publishing Partners**

Crown Agents Zimbabwe work goes from strength to strength

Our work on strengthening Zimbabwe's maternal, newborn and child health (MNCH) systems is set to continue, after we recently signed a contract to roll out Results Based Financing (RBF) across 42 districts in support of the Health Transition Fund (HTF).

Our contract is with Zimbabwe's Ministry of Health and Child Care (MoHCC) and is a progression of the work that we have been carrying out on the revitalisation of the Health Services Fund project that began in November 2012.

This change in funding mechanism now means that the health providers will be paid for predefined and verified results, but the project objectives will remain the same. The overall objective of the HTF is to improve MNCH by strengthening health systems and scaling up the implementation of high impact MNCH interventions through support to the health sector.

We will act as the Fund Holder and National Purchasing Agent. With a team with over 60 people, our responsibilities include contracting assorted service providers, verifying the delivery of the services, paying out against the contracts, capacity building of the MoHCC, and carrying out ongoing evaluation of the RBF model. The new programme is one of the most significant reforms in the Zimbabwean health sector and is currently due to run up to June 2015.

Master of Public Health Graduate looking to give back to her community

Having grown up in Zimbabwe, Chipo Musara decided early on in life that she wanted to pursue a career that focused on helping communities.

Having graduated with a Master of Public Health (MPH) from the University of Liverpool - after studying 100% online - she has set about doing just that through her organisation, RED-UK.

As CEO of RED-UK, Chipo is seeking to improve the livelihood of African immigrants in South Africa and Great Britain through educating individuals once abroad, and at home in her native Zimbabwe. With over 24 years' experience working with minority groups, Chipo's recent studies helped her to pursue her altruistic goals:

Having graduated with a MPH from the University of Liverpool, Chipo Musara is now CEO of her own organisation, RED-UK

'Growing up in a developing country has enabled me to experience the suffering of communities due to poverty, diseases, and ignorance. It has therefore always been my passion to give back to my community by being part of the workforce that helps them, so I have always wanted a qualification such as a MPH to help achieve this.

'The MPH provided me with skills and knowledge; I now have the capacity to design actions to improve public health in communities. So the organisation was formed on what I learnt during my studies.'

Having studied everywhere from in airport lounges to on buses, Chipo graduated on campus in Liverpool this July. Despite describing her studies as 'tough and hard work' she is considering a Doctor in Public Health with the University of Liverpool, and is already confident of the impact her learning has had.

'I am already making an impact in my native country of Zimbabwe. RED-UK aims to change people's lives, and is already doing so in a positive way.'

For more information on the University of Liverpool's 100% online MPH, please visit: http://www.university-liverpool-online.com/mph

Feeling a little faint (answers on page 43)

Part one

Ingrid, a 21-year-old European student on an exchange scheme in your local university fainted in the middle of her final oral examination. Although she recovered quickly and was more embarrassed than obviously ill, one of her examiners, a medic, felt that she looked paler than normal, even for her very fair northern European complexion. Taking her pulse, he found it to be racing, though regular, at 116/minute. She recovered quickly enough to continue with the exam, and did well, but the examiner decided to take her aside and probe a little further into why she might have fainted.

Ingrid admitted that for the last six weeks or so she had been feeling more tired than usual and had been becoming breathless when exerting herself, such as running and even when going upstairs. She had never been ill, her periods had been normal, with no excessive bleeding, and she had been eating her 'normal student food'. She had no neurological symptoms or signs. Her stools were normal and she had not noticed any bleeding. Her parents were still alive and healthy: there was no family history of illness of note. Her blood pressure was normal and she had a BMI of 23, well within the normal range of weight for height. Even after resting for half an hour, her pulse rate was still 110 per minute. A fingerprick blood test showed a haemoglobin of 48g/litre, so she was asked to come into the clinic for further tests. A preliminary blood smear showed a mean red cell volume of 112fL. The red cells were of irregular shape with clear unpigmented central areas, and the slide showed some fragmented red cells, an occasional large nucleated red cell, and large hypersegmented neutrophils.

Q1 What are your preliminary thoughts having seen these results?

(a) She may have serious bone marrow disease and needs admission for further tests.
(b) The short history and apparently otherwise good health suggests a possible dietary cause.
(c) The lack of bowel symptoms tends to rule out malabsorption as a cause.
(d) You must ask about her diet in more detail – what is 'normal student food?'
(e) A lack of neurological signs rules out Vitamin B12 or folate deficiency.

Part two

Q2 Ingrid admits that she 'doesn't like vegetables much' and that her diet consists mostly of fast foods, almost completely without fresh fruit or vegetables. She has been eating like this since she left her home country six months previously. How significant do you think this admission is for your diagnosis and aetiology?

(a) Not at all significant: she is of normal weight and you have no reason to believe that the cause of her anaemia is dietary.
(b) Macrocytic anaemia like this in a young woman is likely to have an endogenous cause such as pernicious anaemia.
(c) Before considering diet as a cause you must consider others such as infection, bone marrow dysplasia, and reaction to drugs.
(d) Her dislike of vegetables is hugely significant in her case.

Part three

Q3 How do you now proceed with investigating and treating Ingrid's macrocytic anaemia?

(a) Without delay give intramuscular vitamin B12.
(b) Give vitamin B12 plus oral folate and iron.
(c) Consider blood transfusion to 'top up her haemoglobin'.
(d) Arrange for malabsorption studies.
(e) Screen for blood levels of drugs that might have caused a macrocytic anaemia.

Part four

Q4 Leaving aside Ingrid's case, which of the following can cause macrocytic anaemia with a blood picture like hers?

(a) Coeliac disease
(b) Inflammatory bowel disease
(c) Pernicious anaemia
(d) Methotrexate
(e) Hypothyroidism
(f) Liver disease
(g) Myelodysplasia

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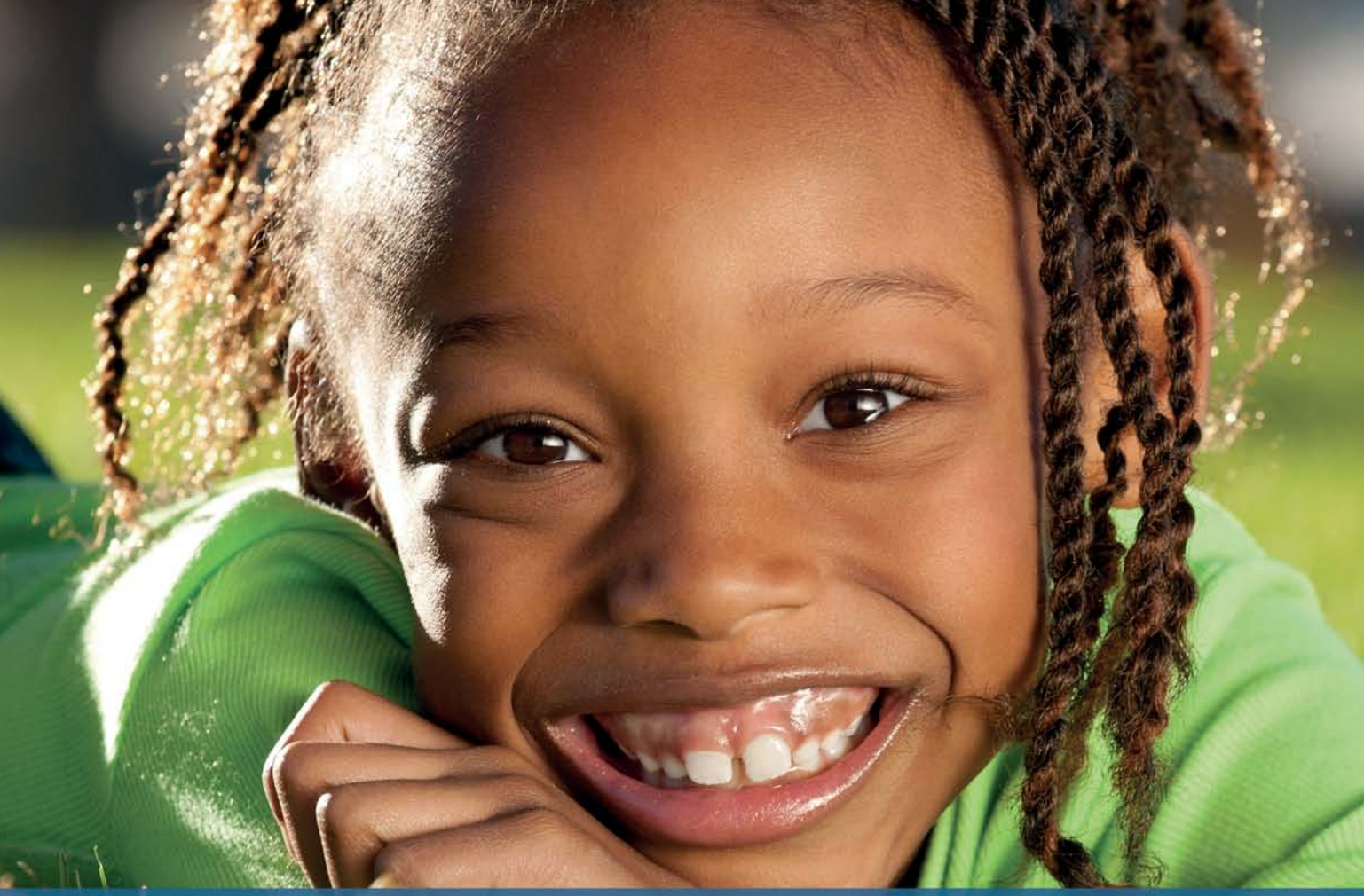

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