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

Pharmacy Review

The international role of pharmacists

It's been a year since I returned from helping in the Ebola epidemic in Sierra Leone, and I have attended two international meetings about the work.

The first was with all the people involved in the Oxford University/Wellcome Trust Ebola trial. The meeting looked at what went well, what could be better, and how things should be done differently.

The international co-operation between the Europeans and the Sierra Leoneans was very encouraging; everybody contributed to the good running of the project. Communication with patients was important as informed consent is required for all clinical trials. The work of the locals is to be commended as they communicated in four or five local languages whilst wearing fully protective personal protection (PPE) suits.

One of the outstanding things was the logistics. There was good co-operation with the USA, UK, and Danish military, and with the Sierra Leone army to ensure that everything arrived in the right place at the right time. One piece of equipment, a portable sterile manufacturing unit (Posidome® manufactured by Banthrax in the USA) was ordered and transported to the treatment centre in less than 10 days.

The second meeting was in Brighton, on the British south coast. It was on the role of pharmacists in humanitarian relief. Once again logistics was emphasised by several of the speakers with examples: one central store had run out of ciprofloxacin 500mg tablets, so orders were not fulfilled. They had an excess of the 250mg tablets, but as they were a different item, they were not being supplied. A second example was about the treatment of tuberculosis (TB). As treatment requires several months of different medication, it is not appropriate to start unless a complete course of treatment is available for each patient. It appears that there wasn't enough medication for everybody, so the stores were supplying some hospitals with one of the required drugs, and other hospitals with the other drug. As a result none of the patients could be treated.

With a pharmacist in the supply chain, both of these problems would be solved. Hospitals would get the ciprofloxacin they needed, and both of the TB treatment centres would get enough of both drugs to treat half of their patients.

One of the delegates reported that as medicine supplies were erratic, the doctors would put the diagnosis on the prescription, and allow the pharmacist to supply anything appropriate; this saved hours of contacting the doctor to change the prescriptions.

One other fact that came from the conference is that when there is not a declared emergency, most health workers can come and practice. Doctors' and nurses' qualifications are internationally recognised, but pharmacists have to qualify in each country and most have to take an exam. Also, the World Health Organization (WHO) emergency relief teams do not have a uniform for pharmacists, or official job descriptions and duties.

International recognition of skills specific to pharmacists is surely required.

Polypharmacy

As people in the so-called developed world live longer, they are more likely to have multiple illnesses. Living longer doesn't necessarily mean having more healthy years.

The term 'Polypharmacy' is given to include patients taking more than four or five medications (or medications taken without an obvious diagnosis). 'Hyperpolypharmacy' has been developed from this to describe patients who are taking 10 or more regular medications.

An article in *JAMA Internal Medicine* looked at medication use in two groups of adults aged 60–85 in 2005 and 2010. In 2005 about 30% of patients were taking five or more medicines, and in 2010 this had increased to 35%. The number of patients with potentially serious drug interactions went up from 8.4% to 15.1%.

A study course 'Polypharmacy' has been written to help sort out some of the problems of Polypharmacy. Part of the cause is that more treatments are being standardised (e.g. for stroke prevention high risk patients are prescribed a statin, an antiplatelet agent and an ACE inhibitor). If a patient has more than one illness with a defined treatment regimen, another three or four medicines could also be prescribed. Patients may also be seen by several doctors, and each may add their preferred medications without clear guidance on stopping or reviewing a dose. Sometimes one medication is prescribed to treat the adverse effects of another; an NSAID (Non-steroidal anti-inflammatory agent, such as ibuprofen) prescribed for arthritis, which causes hypertension being treated with a calcium channel blocker (e.g., diltiazem), which in turn can cause ankle swelling requiring a diuretic. Stopping the NSAID would stop the hypertension and cancel the need for the other medication.

Pharmacists may be the most appropriate person to advise prescribers about the problems of polypharmacy. Polypharmacy may be assessed in seven stages:

Assess the patient: Does the patient have any specific problems with their medicines (fitting them in around mealtimes, opening the bottles, forgetting to take them).

Define the goals of the medication review: What does the patient want? (Not the prescriber or dispenser.) Perhaps the patient just wants fewer tablets to take, or it may be that diuretics are affecting the patient's lifestyle. Stopping the medicines that are not helpful, or changing the timing of others may help.

Identify the medicines with potential risks: The classes of drugs most likely to cause hospital admissions are antiplatelet and anticoagulants, diuretics, and NSAIDs. If the patient is on any of these, and there is no

clear diagnosis, are they really necessary.

Assess the risks and benefits for the individual patient: Is there a medical problem that has resolved but is still being treated? Is the medication prescribed for a condition actually working? Will the patient live long enough to benefit from long-term treatment.

Agree actions to stop, reduce the dose, continue, or start: Agree with the patient what may be the best plan, then communicate with the prescribers. Some patients may not need daily treatment to reduce symptoms, maybe three times a week is enough

Communicate with all relevant parties: All prescribers, the patient, the patient's carers must all be informed appropriately as to the required plan.

If a review is carried out properly the patient will have a better lifestyle, come to appreciate the pharmacist more, and the prescriber will learn more appropriate prescribing practices.

Pain relief

I hope we are all familiar with the WHO pain relief ladder. It was originally published in 1985 as a guide to control cancer pain. The pain ladder has been so successful that it is being used internationally for all types of pain.

For severe pain (step three) the recommendation is to use opioids with or without other drugs to control symptoms (e.g., amitriptyline or gabapentin for neuropathic pain). On several occasions WHO has looked at the availability of opioids in developing countries. The latest report was in January this year which commented that no oral morphine (a WHO essential drug) was available in Egypt, and the alternatives (fentanyl, hydromorphone, and oxycodone) were too expensive for the majority of the population.

The Cochrane database has just revised its guidance on oral morphine. The information is largely unchanged; morphine is still the opioid of choice, and there are few people who cannot tolerate it. The additional information is that modified release morphine preparations can be used to titrate the dose to maximum analgesic effect. There is nothing to suggest that other opioids are better than morphine, and it still remains the opioid of first choice.

It is possible to switch between opioids, and there are various tables of relative potency. There is, however, little agreement of the values. The disagreement about comparative doses is highlighted in an editorial about Morphine Equivalent Daily Dose (MEDD) and Oral Morphine Equivalent (OMEQ). I recently did some work at my own hospital in Norwich in producing an opiate conversion chart, based on the best available information. Even so, the values are approximate, and there is no direct conversion for methadone, a longer acting opioid often used in the UK to help wean addicts.

If one or more opioids are unavailable, some suitable dose equivalents for substitution are:

Oral Morphine 10mg =
Injectable Morphine 5mg =
Oral Codeine (or dihydrocodeine) 100mg =
Oral Tramadol 100mg =
Oral Oxycodone 5mg

Fentanyl and buprenorphine patches are approximately the same potency (measured in micrograms/hour). Fentanyl patches 25 micrograms/hour is equivalent to 60mg morphine daily.

If a patient has to be converted from one opioid to another, a lower dose than that calculated should be used to avoid respiratory depression, and the dose increased as necessary.

We all hope that international legislation will eventually catch up with the WHO essential drug list, and make morphine available to all those who need it.

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Public Health Review

The 2015-16 yellow fever outbreak in Africa

Beginning in December 2015, Angola has experienced its first yellow fever outbreak in 38 years. According to the World Health Organization (WHO), the 1988 incident recorded only 37 cases and 14 deaths.[1] Over 300 people have died in Angola so far this year. Then in March 2016, the Democratic Republic of Congo (DRC) notified WHO of cases of yellow fever in connection with an ongoing outbreak in Angola.[2] Seven hundred suspected and 52 confirmed cases resulted in over 60 suspected yellow fever deaths by early June 2016 in the DRC. Then in April 2016 Uganda notified WHO of an outbreak of yellow fever in Masaka district, south of Kampala.[3]

The public health response is two-fold. The first approach is vaccination, while the second is vector control. The latter is beneficial in controlling other flaviviruses that are also carried by the *Aedes aegypti* mosquito including Zika, dengue and chikungunya.

Vaccinations

WHO clearly advocates that, 'Vaccination is the single most important measure for preventing yellow fever. Yellow fever vaccine is safe and effective and provides immunity within one week in 95% of those vaccinated. Yellow fever control is based on the prevention of outbreaks'.[4] This can only be achieved if the majority of the population is immunised.

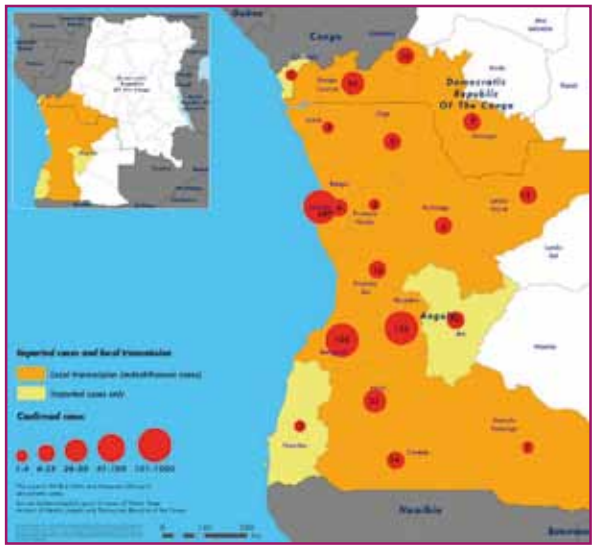
In 2013, WHO revised the yellow fever vaccination schedule. It reported that the 'booster' vaccination given ten years after the initial vaccination was no longer necessary.[5] WHO said that, 'Since yellow fever vaccination began in the 1930s, only 12 known cases of yellow

fever post-vaccination have been identified, after 600 million doses have been dispensed'. While this is good news, the challenge remains in getting those first doses to vulnerable populations where national health and immunisation services are weak.

WHO reported that, 'Between 2007 and 2016, 12 countries have completed mass preventive yellow fever vaccination campaigns: Benin, Burkina Faso, Cameroon, Central African Republic, Côte d'Ivoire, Ghana, Guinea, Liberia, Mali, Senegal, Sierra Leone, and Togo'.[1] A mass vaccination campaign in Nigeria is still underway.

With the success of mass yellow fever vaccination campaigns since 2010 in West Africa, it appears that epidemics are shifting to East and Central Africa where vaccination has not been systematic.[6] WHO notes that now with the new outbreak, 'More than 11 million doses of the yellow fever vaccine have been sent to Angola since February this year and more than two million to the Democratic Republic of the Congo'. Efforts are targeted to high transmission urban areas.

Nature, consulting WHO's Control of Epidemic Diseases Unit, explained that, 'the world's vaccine production - just over 40 million doses annually - should be sufficient to replenish emergency stockpiles and contain outbreaks'.[7] The challenge, according to *Nature*, is that



Confirmed cases of Yellow fever at province level - 2016

Hospital staff line up to receive yellow fever vaccines before seeing patients in Sudan. Photo credit: UN Photo/A. González Farran

the current outbreak could overwhelm global vaccine stockpiles because vaccination rates remain low despite mass campaigns and incorporation of yellow fever into routine childhood immunisation programmes.

WHO says that currently there are only four yellow fever vaccine suppliers worldwide. There are suggestions that smaller vaccine doses would be protective, but it is not clear whether they would offer long-term immunity like the current dosing.[8]

Vector control

In addition to focusing increased vaccination coverage on Africa urban centres, what can be done about the mosquitoes?

Vector control is challenged by the propensity of human beings to create breeding sites for *Aedes aegypti* mosquitoes. It is important to remember though, that *A. aegypti* comes into the picture only as a result of the disease spreading from its normal forest habitat. WHO explains that, sylvatic (or jungle) yellow fever is found in tropical rainforests, where, 'monkeys, which are the primary reservoir of yellow fever, are bitten by wild mosquitoes which pass the virus on to other monkeys. Occasionally humans working or travelling in the forest are bitten by infected mosquitoes and develop yellow fever'.[9]

The current Angolan outbreak therefore is, 'notable due to its urban nature. There has been extensive local transmission in Luanda, prompting the vaccination of more than six million people in the province since February this year. The epidemic has spread to several other major urban settings in the country,' according to WHO.[1]

An immediate concern is that, 'the virus might spread to larger African urban centres, as happened in the biggest previous outbreak, which began in 1986 in Nigeria, which ultimately infected 116 000 people and killed 24 000. Africa's urban populations are now much larger than they were in the 1980s,'[7] with a greater propensity to create breeding grounds for *A. aegypti*.

WHO explains that, 'Large epidemics occur when infected people introduce the virus into heavily populated areas with high mosquito density and where most people have little or no immunity, due to lack of vaccination. In these conditions, infected mosquitoes transmit the virus from person to person'.[9]

According to WHO, 'Historically, mosquito control campaigns successfully eliminated *A. aegypti*, the urban yellow fever vector, from most of Central and South America,'[9] though these gains have not been sustained as can be seen with the current Zika virus epidemic.

In the last Century, *A. aegypti* control in the Americas, especially south of the US border, was quite successful. Campaigns focused on source reduction to remove or empty containers with water where mosquitoes bred and insecticide spraying.[10]

Control can also be achieved by applying larvicides to water storage containers and other places where standing water collects.[9] Involvement of household members is crucial in identifying and cleaning containers. A simple chlorine solution can be effective on the walls of water drums and containers where mosquito eggs are laid, or covering such containers.[11]

In Angola, vector control, including elimination of larval habitats and destruction of adult vectors by

spraying with insecticide, has been implemented, with little observable benefit to date. It may be a matter of too little too late, as vector control is best in preventing outbreaks in the first place.[6] Ironically, Angola had a warning that this vector was a problem in a 2013 dengue outbreak.[12]

WHO makes it very clear that, 'Mosquito control programmes targeting wild mosquitoes in forested areas are not practical for preventing jungle (or sylvatic) yellow fever transmission'.[9] This means that until humans make their own habitats inhospitable to *A. aegypti* or get vaccinated, the potential for reintroduction of yellow fever will always be possible.

Case management

WHO explains that, 'Many people do not experience symptoms, but when these do occur, the most common are fever, muscle pain with prominent backache, headache, loss of appetite, and nausea or vomiting. In most cases, symptoms disappear after three to four days'. A small percentage go on to develop serious, life-threatening disease.[9]

Good supportive treatment in hospitals improves survival rates. 'There is currently no specific antiviral drug for yellow fever, but specific care to treat dehydration, liver and kidney failure, and fever improves outcomes.'[9] In Uganda, case management was an important intervention accompanied by social mobilisation, reactive vaccination and a rapid yellow fever risk assessment.[3]

In conclusion, it is important to recall our present circumstances as outlined by WHO. 'Over the past two decades, the number of yellow fever cases worldwide has increased due to declining population immunity to infection, deforestation, urbanisation, population movements, and climate change.'[5]

These forces are gaining momentum. Community involvement in urban vector control is needed on a proactive basis, as is incorporating yellow fever vaccine into routine childhood immunisation programmes. Greater attention is needed to mass vaccination campaigns, especially in urban areas of East and Central Africa. As a final resort, lives can be saved with timely supportive therapy, exactly as was done with the Ebola epidemic.

A final concern is logistics. We know what works to prevent disease and control vectors. The question is whether public health systems can deliver the vaccines, mobilise communities to control vectors and maintain time surveillance to detect future outbreaks, and respond quickly.

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