

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

Ophthalmology Review

Trachoma

It is some years since I have discussed trachoma in *Clinical Review*. This is not because there have been no advances, but rather because there has been so much research that it is hard to keep up!

The World Health Organization's strategy for reducing blindness caused by trachoma is known by its acronym: SAFE. This includes Surgery for trichiasis, Antibiotics, Facial cleanliness, and Environmental improvement.

The mainstay of community-based antibiotic treatment is azithromycin. This drug is donated to trachoma control programmes by the manufacturer. Azithromycin has many advantages over tetracycline eye ointment. A single oral dose is effective, whereas tetracycline eye ointment must be instilled daily for 6 weeks. Adverse effects of azithromycin are rare, however, everyone who uses tetracycline eye ointment will experience local irritation and blurred vision. It has been shown that a single dose of azithromycin, given to everyone in the community, apart from pregnant women and children less than 1 year old, will eliminate trachoma from that community. Unfortunately, in areas with a high baseline prevalence of chlamydia infection, the disease recurs. At present WHO recommends annual treatment with azithromycin to the entire population in communities with hyperendemic trachoma (prevalence >30% in children). The aim of this is not to eliminate the disease, but to reduce its prevalence to a level that is unlikely to cause blindness. It is hoped that implementation of Facial cleanliness and Environmental improvements will lead to the gradual elimination of the disease in rural Africa in the 21st century, just as they did in Western Europe in the 19th century. The disadvantage of this approach is that azithromycin distribution has to be continued indefinitely. Secondly, although improved hygiene did eliminate trachoma from urban Europe, it took decades. Clinical trials of interventions to improve facial cleanliness or reduce the fly population by spraying insecticide have shown either modest improvement, or no benefit at all at 1 or 2 years. These interventions may well be effective in the long term, but there is no evidence that they will lead to a rapid reduction in trachoma prevalence.

Is elimination possible?

An alternative approach would be to eliminate the

infection, and prevent transmission of *Chlamydia* in the communities. Until recently there were little data to support this approach, and there was no evidence that such a goal is even achievable. A group of researchers in Ethiopia has been carrying out a number of trials of community-based distribution of azithromycin to determine the optimum dosage regime and to test whether or not it is possible to interrupt the cycle of transmission in a hyperendemic area, using antibiotics alone.

The first paper suggests that elimination is possible.¹ The authors report on two villages in which trachoma became undetectable. Initially the authors examined all children aged 1–5 years. Approximately 80% of these children showed clinical evidence of active trachoma infection – i.e. TI (trachoma inflammation) or TF (trachomatous follicles) on the WHO grading scale. Polymerase Chain Reaction (PCR) testing for *Chlamydia* DNA showed that infection was present in 48% of the children in both villages. Azithromycin was then given to everyone in the community, apart from pregnant women and children under 1 year. This was repeated every 6 months for 3 years. The average treatment coverage was over 90% in both villages. Twelve months after the last treatment, the communities were assessed again.

In pre-school children the clinical signs of infection were present in only 17% and 24% in the two villages. PCR did not detect any *Chlamydia* in any child. A modified test, which looks for *Chlamydia* RNA rather than DNA was then performed on all subjects in both villages. Once again, no *Chlamydia* could be detected.

It is unlikely that this dramatic reduction was due to improved hygiene or cleaner faces, as there was no direct intervention to address these issues.

Of course, the follow-up period was only 1 year, and it is likely that, without treatment to all the surrounding villages, migration will eventually lead to recurrence. However, it is quite a convincing demonstration that elimination of infection with antibiotics alone may be achievable.

The biannual treatment approach

The study quoted above was part of a larger trial to examine the benefits of treatment every 6 months as opposed to every 12 months.² In this trial sixteen villages were randomised into two groups of eight villages. In one group everyone was treated once per year, and in the other group azithromycin was given every 6 months. The prevalence was estimated from PCR detection of *Chlamydia* DNA in conjunctival swabs taken from all the children aged 1–5 in the villages. At baseline there was no significant difference in the mean prevalence of infection. In the annual treatment villages it was 42.6% (range 14.7–56.4%), and in the biannual treatment villages the mean prevalence was 31.6% (range 6.1–48.6%). After the first treatment, the prevalence declined to 3–5% in both groups. However by 12 months, the prevalence had risen again to 10.9% in the annual treatment group compared with 1.3% in the biannual treatment villages. At 24 months the mean prevalence was only 0.9% in the villages treated every 6 months compared to 6.8% in the annually treated group

($p=0.03$). In most of the villages treated twice per year, no infection was detected.

The results of this trial suggest that biannual treatment with azithromycin may be more effective than annual distribution. This may seem more costly in the short term. However, if it leads to elimination of the disease, the distribution programme can stop, whereas with annual distribution it is likely to continue indefinitely.

Herd immunity

The same researchers have since started a much larger trial, which is already producing some interesting and valuable results. In this study six groups of villages have been randomised to different interventions, but only three are reported here. Each group contains about 1200 people, of whom half are children in the 1–10 age range. Mathematical models suggest that it may not be necessary to treat all the individuals in a community in order to block transmission of disease. We are familiar with the concept of herd immunity in immunisation programmes, and it may be possible to achieve something similar with community-based distribution of antibiotics, provided those most at risk of infection are all treated.³ For trachoma, this means treating children. One group (control group) received no treatment. Another group (mass treatment) received a single annual dose of azithromycin to the entire community. In a third group, azithromycin was given four times per year only to children aged 1–10 (study group), and adults were not treated. The authors compared the prevalence of trachoma infection by PCR in both children and adults at twelve months in all three groups.

At baseline the prevalence of trachoma infection in children was around 45% in all three groups. In subjects aged 11 or older, the prevalence of trachoma infection ranged from 12.7% to 15.5%. After 12 months of treatment, unsurprisingly the prevalence in children in the study group had declined to 3.6% and in the mass treatment group to 14.6%. This demonstrates that treatment every 3 months is more likely to eliminate childhood infection than annual treatment. However, the more interesting finding was the prevalence of infection in those aged 11 and older. In the mass treatment group, it declined from 13.2% at baseline to 6.2% at 12 months after a single dose of azithromycin. In the study group, in which subjects aged 11 and older were not treated, the prevalence in this group also declined from 15.5% to 8.2%, which is not significantly different from the mass treatment group. In the control group, who did not receive any azithromycin, the prevalence of trachoma in older subjects was unchanged at 12.7%, showing that the decline in the two treated groups is unlikely to be due to a generalised reduction in the prevalence of infection.

This study shows that treating children alone every 3 months appears to be as effective at reducing the prevalence of trachoma infection in adults as treating the entire community every 12 months. It might seem unlikely that more frequent treatment would be any easier or less expensive. However, children aged 1–10 are the easiest group in the community to reach. Adults

are out at work, and there is a significant opportunity cost for them in attending for treatment. In addition, the doses of antibiotic required for children are much lower than those needed for adults.

Benefits of mass distribution

Mass distribution of antibiotics may have undesirable effects, such as inducing antibiotic resistance. However, mass distribution of azithromycin appears to have a very beneficial side-effect. It halves mortality in children aged 1–9.⁴ As part of their study on different distribution strategies for azithromycin, the researchers also examined the effect on childhood mortality. In three groups of villages (treatment group), all children between 1 and 10 years old received azithromycin, either annually, biannually, or quarterly. In the fourth group of villages, treatment was deferred for 12 months (control group). In the control villages, the estimated mortality for children aged 1–9 years was 8.3/1000 person years (95% C.I. 5.3–13.1). In the treated villages, the mortality was reduced to 4.1 (95% C.I. 3.0–5.7). In children aged 0–1, none of whom was treated with azithromycin, there was no difference in mortality, which suggests that the improved survival is more likely to be related to the azithromycin distribution than to a generalised improvement in living conditions. The precise reason for the reduction in mortality is uncertain, however infectious diseases is a major cause of death in Ethiopian children, and it is likely that azithromycin reduced mortality and morbidity from infections.

Spraying regime

Unfortunately the results of clinical trials are not all good news. In a study in Tanzania, researchers examined whether reducing the fly population following mass treatment with azithromycin would reduce the risk of recurrence.⁵ Unfortunately it appears to be ineffective. Sixteen small communities near Kongwa, in central Tanzania were randomly assigned to two groups of eight communities. In both groups the whole community (excluding pregnant women and children <1 year) was given a single dose of azithromycin to reduce the prevalence of *Chlamydia* infection. Pre-school children (<8 years in Tanzania) were identified as the sentinels for the disease. The treatment communities received an intensive programme of insecticide spraying every 2 days for 2 weeks around all the homes, latrines, and cattle pens in the village. A less intensive maintenance phase of spraying every week continued for the rest of the year. The effectiveness of the spraying regime was monitored by fly paper strips in every community to count the number of flies trapped. The fly counts showed significantly fewer flies in the treated villages throughout the treatment period. However fly counts were variable, and tended to be much higher during the short and erratic rainy season. At baseline in the control group 68% of children had clinical evidence of infection and *C. Trachomatis* was detectable in 35% compared to 63% and 29% respectively in the treated villages. After 6 months of fly control and a single mass treatment of azithromycin, *C. Trachomatis* was detectable in 7% of children in the control group and 9% in the treated communities.

At 1 year, 44% of children in the control communities and 43% in the treated villages had clinical evidence of infection. Unfortunately there were no data on the 1 year prevalence of *C Trachomatis* infection as an entire shipment of samples was lost!

A previous study for The Gambia has suggested that intensive fly control may be beneficial. The authors conclude that multiple different mechanisms of transmission may be operating in a hyperendemic area like Kongwa, and that reducing the fly population alone may be insufficient to interrupt transmission. In communities with lower prevalence, such as The Gambia, flies may play the major role in transmission and fly control has a correspondingly greater effect. At present there is insufficient evidence to support intensive insecticide spraying as a strategy for controlling trachoma. However, environmental measures which reduce the fly population (e.g. proper waste disposal, use of latrines, etc.) have many other beneficial effects and should be encouraged.

At present there is still uncertainty about the best way to use antibiotics to control trachoma. However more evidence is accumulating every year, and I am sure that we will have an effective evidence-based strategy within a few years.

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Africa HEALTH CPD Challenge
See page 69 for questions about this article

STI Review

HPV update

The World Health Organization (WHO) has prequalified two vaccines against human papillomavirus (HPV). In May 2009, the organisation accepted Merck's bivalent *Gardasil*® vaccine, and in July 2009, it accepted Glaxo-SmithKline's quadrivalent *Cervarix*® vaccine.¹ Prequalification means the vaccines meet the requirements of quality, safety, and efficacy of United Nations agencies and enables UN agencies and the GAVI Alliance to purchase the vaccines in partnership with developing

countries. These vaccines prevent infection with HPV types that can lead to the development of cervical cancer. *Gardasil*® offers protection against oncogenic HPV types 16 and 18, while *Cervarix*® covers types 6, 11, 16, and 18. HPV types 16 and 18 account for about 70% of all cervical cancers worldwide, and types 6 and 11 are responsible for more than 90% of anogenital warts, a substantial proportion of low-grade cervical dysplasia, and recurrent respiratory papillomatosis. HPV infection is also associated with vaginal, vulvar, penile and anal cancers, as well as some cancers of the head and neck.

WHO recommends that HPV vaccination be introduced into national immunisation programmes where prevention of cervical cancer is a priority, where it is programmatically and economically sustainable, and where its 'cost-effectiveness aspects have been duly considered.'² While these are rational recommendations, their practical application is complicated. While research has shown the two vaccines to be very effective against their specific HPV DNA genotypes, there are many other issues that affect their ability to reduce cancers and other HPV-related diseases within a population.

One major factor is the prevalence of specific HPV genotypes within a population. More than 100 HPV types have been identified, and about 40 can infect the genital tract. Fifteen of them have been ranked as high-risk types (HPVs 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82), and the other 3 have been classified as probable high-risk types (HPVs 26, 53, and 66).³ Several recent studies show that the frequency of HPV genotypes in Africa differs from that found in the United State and Europe. A study of 1073 women in South Africa found cervical HPV prevalence ranged from 20.4% among women with normal cytology, to 41.7% among women with atypical squamous cells of undetermined significance (ASCUS), to 70.2% among women with low-grade squamous intraepithelial lesions (LSILs), and 83% among women with high-grade squamous intraepithelial lesions (HSILs).⁴ HPV types 16 and 35 were most common among women with HSILs. A study in Conakry, Guinea found HPV type 16 was the most common type found in cervical specimens from 831 women in the general population (7.3%), as well as among 77 samples from women with invasive cervical cancer (48.6%).⁵ Types 45 (18.6%) and 18 (14.3%) were the next most common types found among women with invasive cervical cancer. The authors conclude at least 63% of cervical cancers are theoretically preventable by vaccination with against HPV types 16/18 in Guinea. In Bioko, Equatorial Guinea, a small study found that 15 of 25 women with cervical lesions were positive for HPV (60%).⁶ HPV genotypes 16 and 33 were identified in four cases each, HPV 58 in two cases, HPV 18, 31, 52, and 82 in one case each, and coinfection with HPV types 16 and 58 in one case. Vaccination against HPV types 16, 33, 58, 18, and 31 would be most effective in this population. Among cervical samples taken from 2040 women in Zimbabwe, 24.5% were positive for any HPV type, and 16.1% for an oncogenic type.⁷ HPV 58 was the most common type identified. Among female sex workers

in Kenya, high-risk HPV types were 3.6 times more common among those who were HIV-positive.⁸ In decreasing order, the most prevalent high-risk HPV types among HIV-positive women were 52, 16, 53, 18, 35, and 66, while for HIV-negative women the order was HPV 16, 59, 35, 52, 66, and 53. HPV types 16 and 18 were found in 42.7% of women with LSIL and 42.3% of those with HSIL lesions. However, high-risk HPV types other than 16 and 18 were even more common among those with LSIL (74.7%) and HSIL (84.6%). A study of HPV infection among heterosexual men presenting for voluntary HIV counselling and testing in South Africa found 78% had anogenital HPV DNA.⁹ HPV types 6, 11, 16, and 18 were found in 81% of all HPV-positive men, and HIV seropositivity was significantly associated with multiple HPV infections.

These study results indicate that vaccination against HPV types 16 and 18 would clearly have an impact on cervical cancer in Africa. However, a substantial proportion of HPV-related disease would not be prevented by the currently available vaccines, nor would the vaccines benefit women already infected with high-risk HPV types. As always, the benefits of vaccination and screening programmes must be weighed against their costs. Who should be vaccinated and when? Who should be screened and when? How can these populations be most effectively and efficiently reached? There are no definitive answers yet for African populations.

To be most effective, the HPV vaccines must be given prior to exposure to the virus through sexual activity. This requires developing programmes to reach adolescents and preteens, yet these groups do not normally visit healthcare providers unless they are ill. A recent qualitative study on preparing for HPV vaccination in South Africa found community members thought the optimal age to vaccinate girls was between 9 and 15, and reaching these girls would require a coordinated effort involving sexual and reproductive health, adolescent health, immunisation, and cancer prevention programmes.¹⁰ Vaccinating girls at school, as well as at clinics, could increase coverage, but respondents thought the vaccine should be marketed as preventing cervical cancer, not STIs. Interviewees thought it would be valuable also to vaccinate boys, but many doubted that boys would accept a vaccine for 'reproductive health', something normally associated with women. Indeed, although the quadrivalent *Cervarix*[®] vaccine recently was approved for use in males in the United States, the majority of studies have found many obstacles to vaccinating boys, including low cost-effectiveness, and poor knowledge of HPV and related disease among boys. However, given the goal of reducing HPV prevalence in a given population, vaccinating girls and boys may become the most acceptable and cost-effective way to reduce HPV-related disease, especially if the HPV vaccine can be combined with other routine vaccines.

Given that the incidence of invasive cervical cancer in sub-Saharan Africa is among the highest in the world – estimated at 31.0 cases per 100 000 women, or more than three times the incidence in most more developed countries – there is clear need to make the

best use of available technologies to prevent cervical cancer-related morbidity and mortality.¹¹ Screening for cervical abnormalities is one of the most effective ways to identify and treat early cervical cancers, and is especially important in secondary prevention among those not protected by vaccines. Screening coverage varies considerably by country. A 2008 study of data from 57 countries showed about 1 in 20 women in developing countries is screened for cervical cancer, and older and poorer women, who have greater risk, are least likely to be screened.¹² In sub-Saharan Africa, screening coverage ranges from 2.0% to 20.2% in urban areas and 0.4% to 14.0% in rural areas.¹¹ While Papanicolaou screening tests have been used effectively in more developed countries, they require significant human and laboratory resources, and more cost-effective methods, like visual inspection with acetic acid (VIA) make it feasible to screen and treat more women in resource limited situations. HPV DNA testing also requires significant laboratory resources (although new HPV DNA tests should soon be available that permit field testing), but studies show that women can also obtain their own vaginal samples for testing, thus avoiding a pelvic exam for those who would otherwise not be screened.¹³

Following analysis of research study and pilot project findings, the international Alliance for Cervical Cancer Prevention (ACCP) has concluded that effective cervical cancer screening and treatment programs in low-resource settings should focus on screening 30–39-year-olds using either VIA or HPV DNA testing, followed by cryotherapy treatment.¹⁴ All women should be screened at least once in their lifetimes and offered immediate treatment for precancerous lesions. Pilot studies have shown that physicians and nurses can be trained to provide VIA screening and cryotherapy, but this requires effective training and available equipment.

These recent advances in vaccination, sampling, screening, and treatment of HPV-related disease offer great opportunities to reduce morbidity and mortality, especially due to cervical cancer among women in Africa. There will doubtless be more discussion in the months ahead on how to best and most broadly apply these and other new technologies in specific populations.

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Surgery Review

To err is... surgical?

We never like to admit mistakes, particularly in surgical practice. The fact that they do occur is common knowledge but until now not much has been done in concrete ways to minimise their effects.

We can all remember incidents which should not have occurred in the 'peri-operative period' and which led to unfavourable outcomes.

Following several studies in UK, e.g. the CEPOD – the Confidential Enquiry into Peri-Operative Deaths – we have become much more aware of avoidable factors relating to surgery which can be corrected and lead to a decrease in unnecessary deaths.

In order to understand this problem better the World Health Organization (WHO) set up a worldwide study on how to improve morbidity and mortality in the period from operation to 30 days thereafter. An excellent summary on this vast study¹ is the subject of part of this forum.

I was fortunate to work in two hospitals in Scotland last year, which had already implemented WHO's proposals. From this direct experience I investigated to find out how it had all come about.

The simple statistics are stark and make for sobering reading. A global estimate of how many major surgical procedures are carried out annually suggests 234 million. From this figure an estimate was attempted of the complications from such surgery – deaths and major incidents.

From then the guesswork and estimates stopped. WHO mounted a study in which eight hospitals in different countries took part in a scientific study of a check list of safety features to be used from the anaesthetic room to the recovery period and ward.

In summary, what was designed was a check list similar to that used in civil aviation, in which 19 items were specifically checked before proceeding with any operation. These items range from the very obvious – patient's name, age and date of birth, operation to be undertaken, right or left side – to allergies and the need for blood.

Integral to this process was the concept of checking in three stages:

- Sign in – anaesthetic room before induction of anaesthesia;
- Time out – patient anaesthetised but before skin incision;
- Sign out – before patient leaves the operating theatre.

This study was detailed and the aim was to use the check list, and find out the change in measurable parameters, e.g. death within 30 days of operation and major complications.

The scientific data collected were validated and led to the decision to recommend the check List for general use. This might seem a very grandiose aim but it is one which is achievable.

When I was involved in this process it was immediately obvious how useful and sensible it is. There are various terms used to replace the bland 'check list', such as 'surgical pause'.

The final check list developed has 19 items and in the correct scenario there is one co-ordinator for the whole process. However, in my experience it develops team work and co-operation – particularly when new staff members (as I was then) arrive.

Apart from a service tool, the hope is that many hospitals will use the full check list and correlate their results before and after use. This is surely a surgical advance of a major kind without the need of high-powered technology. The method is to be introduced to England and Wales in 2010. From my own experience it is an innovation of the greatest value. This article is a must for ALL hospitals.

Prophylactic antibiotics in severe burns

We all know that burns are a problem – particularly so on the African continent (and in the southern part even more so). Cold winters, open fires, paraffin stoves, and poorly controlled epilepsy make these injuries a regular event.

We also know that the two main causes of death are early fluid and electrolyte losses, and infection. The latter is an ongoing problem, as could be expected with an unhealed open wound.

The debate regarding local treatment of the burn wound, i.e. to dress or leave open, still continues. But the other major treatment option is, of course, antibiotics. As routine they are always used at the beginning of treatment – more so if the burn is deep and extensive. But are they doing what we expect?

A recent excellent article² puts this subject in a current context. The authors studied the evidence of antibiotic use in severe burns – severe being defined as more than 19% deep.

Contrary to what might be expected it is not always satisfactory to give lots of antibiotic without control.

In fact the very concept is difficult. Prophylactic these days means a short course, parenterally, the first dose being given before the first incision. This is obviously not possible in burns. Therefore antibiotics given when the patient is admitted cannot strictly speaking be prophylactic. So when are they prophylactic – before the first surgical debridement? This could be any time from 4 days to 2 weeks, according to the patient's general condition; or perhaps before each debridement or skin graft.

The authors studied practice in this regard and found very little clinical evidence of what a correct regime would be. To give antibiotics continually to all severely burned patients is to risk outbreaks of resistant organisms in a burns unit – as has happened. In a condition where removing dead skin is a priority but not always immediately achieved, there is always a culture medium for bacteria. Of those studies carried out, only a few followed strict criteriae and in those the results were not conclusive.

What is quite clear is that as in all prophylactic regimes, the doses, routes, and duration must be strictly followed. In this way the patient will benefit from their use and not suffer the consequences of resistant organisms. Also the ward or unit will not have outbreaks of resistant organisms due to cross infection.

More closely controlled studies are needed. The authors of this article from the USA and Switzerland state that due to the 'small number of cases available' better data are difficult to achieve. This is not so in Africa. Unfortunately we have plenty of burns and could carry out such investigations. The results would be beneficial to all.

Oesophageal cancer

There are few parts of Africa where oesophageal cancer does not occur. In many countries it is a very common tumour and one which is almost impossible to cure and difficult to palliate.

There is a distinct variation from the tumour in Africa and that in the rest of the world – particularly Europe and North America. In these countries the tumour is commonest in the lower third followed by middle, then upper third.

In Africa the commonest site for oesophageal cancer is middle-third. Most patients present with advanced disease and curative resection although feasible is almost impossible due to later recurrence.

How to manage such patients? We have long passed the era of gastrostomy. That was found to be a poor way to assist patients. Since most have advanced disease, palliation involves assisting in the most basic functions – that of swallowing – particularly saliva and fluids to maintain hydration.

The usual solution is a tube passed through the tumour. Where should this be done? Can most district hospitals carry this out safely? That this is possible is shown by a recent article from the UK in which a District Hospital studied their practice and results in 57

patients. Their study showed that no patient was operable on presentation – many for reasons of co-morbidity and most from extent of disease.

This non-specialist unit – similar to most district or mission hospitals in Africa – carried out intubation of the lesion without any operative deaths and in several cases, repeated the procedure as required from repeat obstruction.

I found the classification of dysphagia useful and it was used as a yardstick of benefit following the intubation. This is the Mellow and Pinkas classification as follows:

- Grade 0 – no dysphagia.
- Grade 1 – able to swallow some solid food.
- Grade 2 – able to swallow semi-solid food.
- Grade 3 – able to swallow liquids only.
- Grade 4 – complete dysphagia.

Of the 57 patients treated in this series the following results were noted:

- After the operation to place a tube, out of six patients in Grade 4 only one was unable to swallow.
- In Grade 3, 22 could swallow fluids and semi-solid food; only 2 could not.
- In Grade 2, 29 could swallow as above and 3 could not.
- In Grade 1, all could swallow fluids and semi solid food.
- In Grade 0, all 19 could continue to swallow following insertion of the tube.

In terms of diagnosis most were adenocarcinoma (34 cases); there were squamous carcinomata in 16 cases and 1 benign stricture. There was also a scattering of other diagnoses, e.g. extrinsic compression from lung cancer, salivary tumour, and non-Hodgins lymphoma. These were also inoperable cases but also required relief from intractable dysphagia.

The procedure of passing a tube through the tumour is so vital that this should be an operation frequently learned. It is not difficult to do but there are several important points. There should also be available a tube that is readily available and not too expensive.

This short paper is valuable in showing what is possible in this very difficult condition.

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The logo features the text 'Africa HEALTH' in white on a dark blue background, with a yellow sun icon above 'Africa'. To the right, 'CPD Challenge' is written in white on a purple background. Below this, a yellow banner contains the text 'See page 69 for questions about this article'.