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HAEMATOLOGY
CURRENT ISSUES

CONTENT

Cover: Laos

HAEMATOLOGY

Haematological conditions are common in daily practice of tropical medicine; many patients present with some degree of anaemia, by far the most common haematological problem. Anaemia is always the result of an underlying condition, infections such as malaria being the most common, especially among children. In addition, many otherwise 'healthy' people have haemoglobin levels below what is considered normal.

Iron supplementation is one of the most commonly prescribed therapies to correct iron deficiency related anaemia; it is cheap, widely available and usually well tolerated. However, iron supplementation has been the subject of debate. The increased susceptibility, particularly for malaria, may require a more comprehensive approach including malaria control.

In the past, sickle cell disease was typically restricted to the tropics, but nowadays it is spread worldwide. The disease arrived in the Americas and in the Caribbean during the slave trade and more recently in other regions via migration. It is a strange twist that patients may have severe morbidity, whereas carriers contribute to the persistence of the mutation due to the partial immunity it provides to malaria.

In the Netherlands, the number of patients with sickle cell disease has increased in recent years. Over time, care has improved considerably with seven specialized centres collaborating in a multidisciplinary team including clinicians, geneticists, social workers and psychologists. A comprehensive approach has been developed that includes active follow-up, neonatal screening and research. Hopefully, this model can be introduced to LMICs, where treatment is often symptomatic, including repeated blood transfusions.

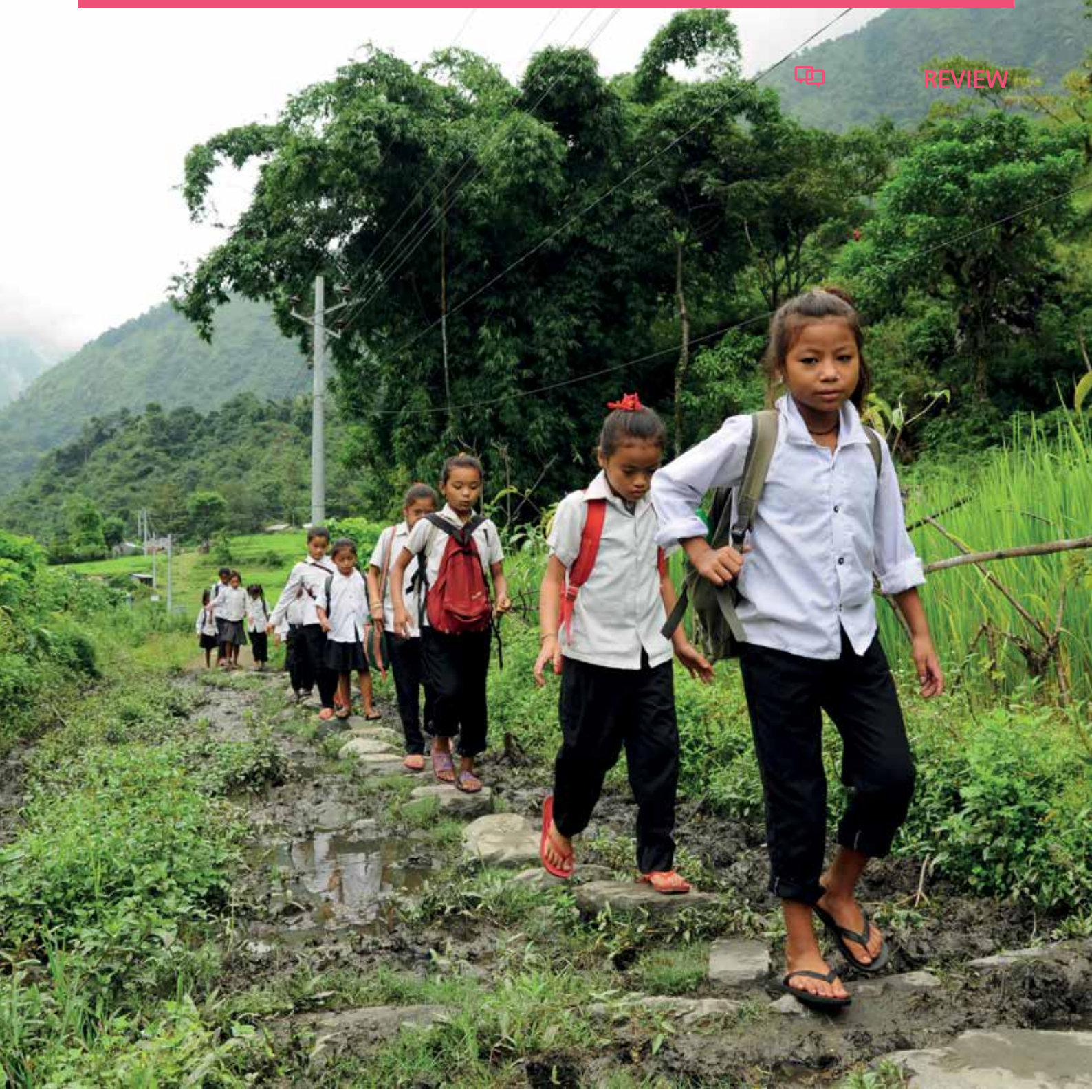
Another common clinical problem that puts a drain on blood transfusion resources is pancytopenia, a neglected clinical entity in which red cell, white cell and platelet production is reduced causing anaemia, infections and bleeding complications. It is difficult to manage in LMICs, as diagnostic capacity is often limited and the underlying cause is therefore not treated. As a result, multiple repeated blood transfusions are given with associated risks.

Safe blood transfusion is therefore among the greatest needs in many LMICs. The Malawi Blood Transfusion Service (MBTS) was established 14 years ago. Public beliefs around blood donation, identifying voluntary blood donors, screening for infections, outreach to communities, and funding are among the challenges the MBTS faces. Nevertheless much has been achieved. Many of us who worked in the tropics will have experienced problems of non-availability of blood or screening tests, such as for HIV, resulting in the horror scenario of transfusing unscreened blood.

Similarly, great advances have been made in relation to childhood malignancies, of which Burkitt lymphoma is the most common. Close collaboration between Malawi and the Netherlands proved very successful. One lesson learned is the importance of an adapted approach to management in LMICs, including research for better treatment. As a result of work done in recent years, cure rates have improved considerably.

Haematology has gained a firm place in the scientific literature. Successful collaboration and research has led to improved understanding and management of common conditions. The articles in this edition clearly show the interrelationship between various haematological conditions and their management (e.g. malaria, anaemia, iron supplementation), including the need for safe blood. They also discuss the specific needs of LMICs, both in clinical medicine and public health.

ED ZIJLSTRA, JOSEPHINE VAN DE MAAT AND JAN AUKE DIJKSTRA



DARJEELING, INDIA Children go home from school (2010).

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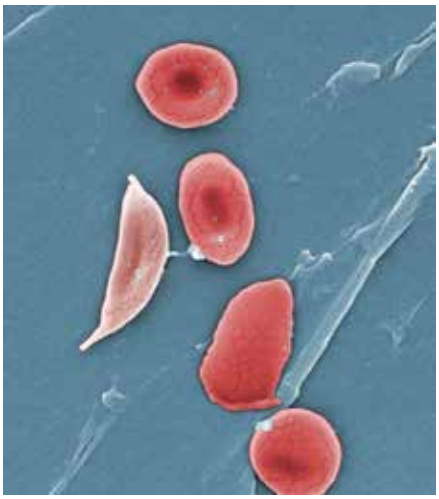
Sickle cell anaemia in children

In 1910 Herrick was the first to describe 'peculiar elongated and sickle-shaped red blood corpuscles' in a patient presenting with respiratory distress and severe anaemia, currently known as sickle cell anaemia (SCA).[1] Worldwide it is the most common congenital haemolytic anaemia, affecting an estimated 4.4 million patients. Roughly 300,000 infants are born with SCA each year, the majority in sub-Saharan Africa but also in India, Saudi Arabia and some Mediterranean countries. Migration brought this heritable disease to the Caribbean region (slave trade), the Americas and the rest of the world.

GENETICS AND PATHOPHYSIOLOGY

Haemoglobin, the oxygen-carrying protein in blood, consists of a tetramer with 2 α- and 2 β- globin chains. A gene mutation on the short arm of chromosome 11 is responsible for the replacement of glutamic acid by valine in the β- globin chain of the haemoglobin (β^s). Upon red cell deoxygenation, this HbS haemoglobin polymerizes into insoluble intracellular fibers causing the sickle cell deformity resulting in membrane damage and ultimately haemolysis. The homozygous form (HbSS or $\beta^s\beta^s$) reduces the red cell life span from 120 to ± 20 days causing anaemia despite increased bone marrow activity.



Sickle cell in a blood smear

Heterozygosity for β^s (HbAS or sickle cell trait) is the mostly asymptomatic carrier state with a survival advantage in areas with high presence of malaria. Other forms of sickle cell disease with variable severity result from combinations of β^s with for example haemoglobin C (HbSC or $\beta^s\beta^c$) or thalassemias ($\beta^s\beta^0$-thalassemia or $\beta^s\beta^+$-thalassemia), or the so called compound heterozygous states.

The microvascular perfusion of vital organs is impaired by a cascade that is set in motion by damaged sickle cells. As they become dehydrated, inflexible and abnormally adhesive, interactions between red cells, activated leukocytes, platelets and vascular endothelial cells occur. A complex interplay between plasma factors, increased expression of adhesion receptors, a pro thrombotic state and endothelial dysfunction will ultimately result in both micro- and macrovascular obstruction resulting in ischaemic organ injury with accumulating loss of function.

Two cases are presented demonstrating the impact of SCA.

CASE 1

A 2 year old boy visited Curacao on vacation from Surinam presented at the paediatric outpatient clinic with swollen and extremely painful hands and feet since one day. No fever or trauma was reported. His past medical history was uneventful. On examination he had a temperature of 37 ˚C, was alert, in a well hydrated and nutritional state and almost continuously crying. The dorsum of both hands and feet were painful, cushiony, and swollen with pencil like fingers. Joints were not affected, no edema was noticed, No signs of meningism, heart and lungs normal, abdomen liver and spleen not palpable. Based on the typical presentation of dactylitis ('hand-foot syndrome'), he was admitted for intravenous hyperhydration and analgesic treatment. The diagnosis was confirmed by high pressure liquid chromatography (HPLC): sickle cell anaemia HbSS. He recovered within 3 days.

CASE 2

A 4 year old boy was rushed to the emergency policlinic by his parents. Sadly he was found dead on arrival. The history revealed that he had been referred to the paediatric policlinic 2 years ago with the diagnosis of HbSS. The family had an illegal status on Curacao and preferred to keep a 'low profile' to avoid extradition to Haiti, their country of origin. Regretfully, healthcare insurance is impossible for illegal citizens, which was yet another reason for them not to visit the paediatric outpatient clinic. Although the boy had fever for 2 days and became lethargic, no medical care was sought. No vaccinations or any other medications were previously administered.

Post mortem examination revealed *S. pneumoniae* sepsis with meningitis. No pneumococcal sub typing was performed. SCA HbSS was confirmed.

COMMENT

Case 1: dactylitis, vaso-occlusive ischaemia and infarction of metacarpals and phalanges, is often the first clinical sign of SCA in paediatric patients under 5 years of age. New-born screening, now implemented in many countries, could have detected the disease right after birth with the possibility of early information to the parents and timely implementation of preventive measures such as pneumococcal vaccination.

Case 2: overwhelming sepsis and meningitis due to especially encapsulated micro-organisms are - although less frequent - still major complications in SCA patients. The main cause is a process of auto-splenectomy due to infarction of the spleen with loss of its filtration function, starting 3 months after birth and completed at around 5 years of age. Daily penicillin prophylaxis for children with SCA was introduced after this intervention was found to make a remarkable difference in sepsis morbidity and mortality. For qualifying patients, prophylaxis was adjusted to a shorter period (5 years) after new studies showed this was reasonable.[2,3]

Both cases highlight the importance of early detection and thorough information about the disease with regular follow up at a paediatric-haematologic facility.

SCA VARIABILITY

One of the most striking observations in SCA is the clinical heterogeneity of the disease between patients within a family, regions and countries, based on a wide variability of phenotypes that sometimes hardly show any symptoms. The combination with α-thalassemia may decrease the severity of specific SCA related complications, whereas worsening others. A persisting high percentage of haemoglobin F (HbF) is by far the most powerful modifier of SCA, as this reduces the sickling process. Patients with the 'high persistent foetal gene' often have more than 20% HbF and are generally less affected by the

disease.[4] Therapy with oral hydroxyurea is aimed at increasing HbF.

SYMPTOMS AND COMPLICATIONS

- Vaso-occlusive (pain) crises (VOC) occur in bones of hand and feet of younger children; 7 years and older in long bones and vertebrae, usually without any physical signs. Triggers are dehydration, cooling off, infections, and 'unknown'.
  Although far less common, avascular necrosis (mostly in femoral heads) should be excluded as well as osteomyelitis that may occur in any bone (often Salmonella and Staphylococcus species).
  VOC in the mesenteric vessels may also cause abdominal pain mimicking acute appendicitis.
- Infections due to loss of splenic function. This immune vulnerability requires that febrile patients should be evaluated without delay to exclude any signs of sepsis, pneumonia and meningitis and be started on broad spectrum antibiotics immediately, awaiting lab results.
- Splenic sequestration in the first 5 years of life, as a result of sudden massive trapping of erythrocytes in the splenic sinusoids, with (increased) enlargement of the spleen causing severe anaemia, hypovolaemia and possible shock.
- Transient aplastic anaemia caused by human parvo virus B19 infection, which by temporarily interfering with erythrocyte production in the bone marrow may result in severe anaemia in patients with an already reduced erythrocyte lifespan. Erythrocyte transfusions are life-saving.
- Acute chest syndrome is an acute pulmonary disease in patients with SCA, often accompanied by fever, chest pain, dyspnoea or tachypnea. Chest X-rays may show a new pulmonary infiltrate. In young children there is often an association with viral respiratory infections. Treatment is mainly supportive. The aetiology is not fully understood.
- Stroke (ischemic more than hemorrhagic) may occur due to occlusion or haemorrhage of large intracranial vessels, sometimes preceded by transient ischemic attacks. MRI and MR-angiography are required to determine the extent of affected brain tissue. Immediate (exchange) blood transfusions are critical in limiting further damage, while chronic transfusions may lower the rate of recurrence by decreasing the amount of HbS below 30%. Transcranial Doppler (TCD) examination may identify children with a high risk of stroke (blood flow velocity in de medial cerebral artery > 200 cm/sec.).
- Cholelithiasis with bilirubin gallstones is a common complication in children with SCA and should be ruled out in any event of abdominal pain. Symptomatic gallstones probably require elective laparoscopic cholecystectomy to avoid cholecystitis.
- Priapism, a painful erection of the penis lasting longer than 4 hours is a medical emergency. Treatment with epinephrine, hyperhydration and analgesics as well as aspiration and irrigation of the corpora cavernosa are used for fast relief.
- Retinopathy with possible loss of visual acuity is mainly seen in older children (>10 years) with HbSC. Retinal artery occlusion may cause a proliferative retinopathy, vitreal haemorrhage and retinal detachment. Laser photocoagulation may prevent further damage.
- The renal medulla with high osmolarity facilitates erythrocyte sickling with vaso-occlusion of the vasa recta, causing loss of urine concentration with polyuria, promoting dehydration and enuresis. Papillary necrosis due to renal ischaemia may lead to haematuria.

TREATMENT

More than 100 years of sickle cell research has resulted in a much deeper insight into the pathophysiology of SCA.

Besides hydroxyurea as the currently most effective and available medication, several disease modifying drugs are currently in the pipeline. These are targeted at cell adhesion, inflammatory pathways, up regulation of HbF, haemoglobin polymerization and sickling, coagulation and platelet activation.[5]

At present, the only cure for SCA is hematopoietic stem cell transplantation, but this procedure is limited by the frequent lack of an HLA compatible donor and a possible graft versus host rejection. In general, this option is therefore limited to those with severe complications of SCA.[6]

SUMMARY

SCA is a disease with a widely variable phenotype. Guidelines should therefore be adjusted and reflect the local experience with disease severity and complications. [7] The ultimate cure should be easy to apply all over the world (also cost wise, as the majority of patients live in areas with a lower socio-economic status). In the meantime, prevention - family planning/counselling, newborn screening, regular medical follow up (TCD and retinopathy screening), increased infection risk awareness and vaccination (conjugated pneumococcal vaccine), optimized hydration status, avoiding hypoxic environments and strong cooling off - is still our best bet, as this may decrease morbidity and improve life expectancy.

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Routine comprehensive care for patients with sickle-cell disease in the Netherlands

Sickle-cell disease (SCD) is an autosomal, recessive haemoglobinopathy and multisystem disorder characterised by episodes of vaso-occlusion, ongoing haemolytic anaemia and progressive organ failure. It is the most common monogenetic disease worldwide with an estimated 350.000 births annually affected and recognised as a global public health problem by the World Health Organization (WHO).[1] The global distribution of the sickle haemoglobin (HbS) allele is indicative of the protective effect of sickle cell trait (HbAS) against Plasmodium falciparum malaria, first described by Haldane in 1949.[2,3,4] However, migration from malaria-endemic regions to Northern America, Western Europe and Australia has led to spreading of the HbS allele far beyond its origin.[5] Roughly 2500 individuals in the Netherlands currently have SCD, of which 1000 are children, and the carrier incidence is 0.4%.[6] Most of those affected are of Surinamese, Asian or African ancestry, with a minority being of Afro-Caribbean or Middle Eastern descent.[7]

Seventy five percent of the global burden of SCD occurs in sub-Saharan Africa, where the majority of children with the disease do not reach their fifth birthday.[1,8] In contrast, the life expectancy in well-resourced countries has significantly improved with almost all infants now expected to survive into adulthood because of comprehensive care programs.[9,10] However, the average life expectancy of patients with SCD is still 20 years less than that of healthy adults.[11]

This article aims to provide insight into the characteristics of routine comprehensive care for patients with SCD in the Netherlands, with a special focus on paediatric aspects. It does not, however, provide a summary of the management of SCD, which is excellently reported in the guideline of the National Heart Lung and Blood Institute (NHLBI).[12]

NEONATAL SCREENING

Prompt diagnosis is the first step in improving treatment outcomes of individuals with SCD. Early diagnosis, before clinical symptoms occur, allows for the enrolment in comprehensive care programs and education of parents on the recognition of danger signs and importance of vaccinations and prophylactic antibiotics.

Increased migration from sickle-cell endemic countries to the Netherlands resulted in initiation of a universal newborn screening program for SCD in the Netherlands on 1 January 2007.[13] Diagnosis is established by high-performance liquid chromatography (HPLC), which has a high sensitivity and specificity and a positive predictive value of 100%. In addition, only a small blood sample is required and other inherited blood disorders such as severe α- and β- thalassemia are concomitantly diagnosed by this method.[14]

When a carrier of HbS is identified, both parents and the general practitioner (GP) receive a letter explaining the test results, except for parents who have indicated that they do not want to be informed about the carrier status of their child (opting out). Parents are then invited for an informative consultation about SCD and carriership. GPs are advised to emphasise the importance of testing both parents for haemoglobinopathies and to refer couples at-risk to a clinical geneticist. Knowledge of this risk allows for a range of options, including prenatal diagnosis and limiting of family size.

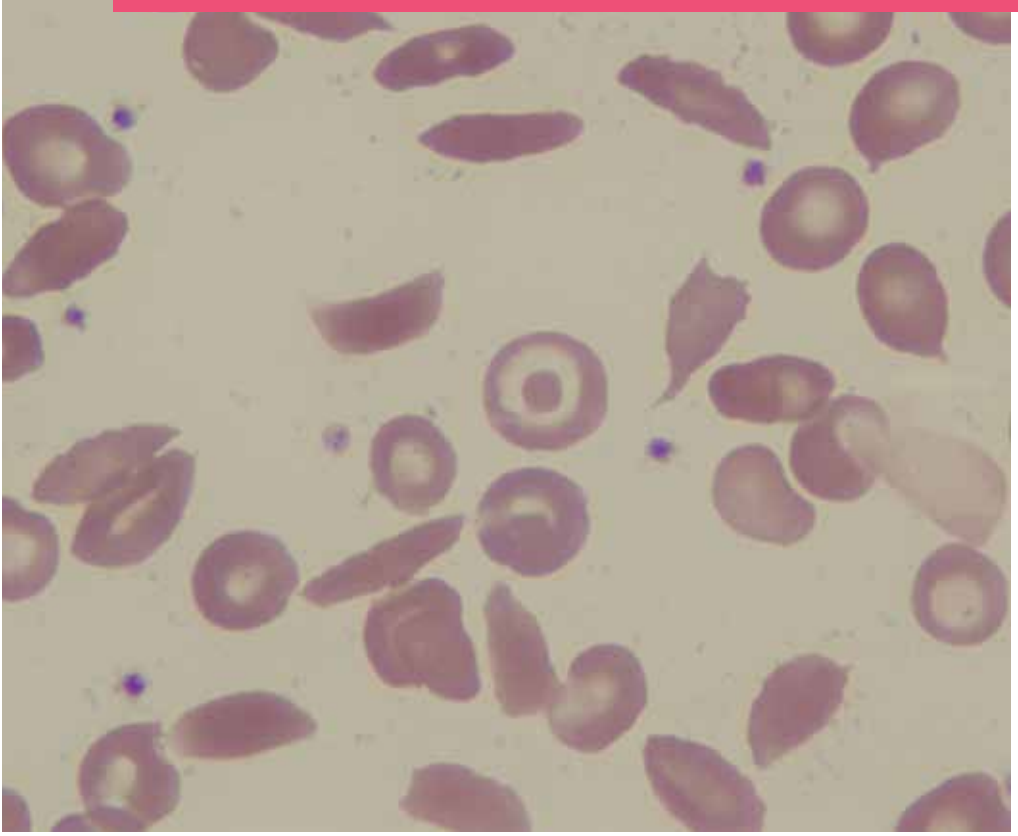
VACCINATION AND ANTIBIOTIC PROPHYLAXIS

Children with SCD are particularly at increased risk of severe bacterial infections due to an impaired splenic function. Prior to the initiation of neonatal screening for SCD, infection by encapsulated organisms was the leading cause of death in afflicted children.[16] In addition to routine courses of immunisations according to national schedules, yearly vaccinations against influenza from the age of 6 months are administered as well as repetitive pneumococcal vaccinations. Furthermore, all SCD patients receive twice-daily prophylactic penicillin from the age of 4 months until their twelfth birthday.

However, one-third of the children newly diagnosed with SCD are immigrants and not born in the Netherlands.[5] Unfortunately, those children are not systematically screened for haemoglobinopathies and are therefore at high risk of life-threating complications before the diagnosis SCD has been made. This is a disparity in healthcare and therefore the initiation of other screening programs is currently being considered (i.e., in health screening package offered to immigrants).

SPECIALISED SICKLE- CELL CLINICS

It is recommended that all patients diagnosed with SCD are referred to a (paediatric) haematologist with expertise in haemoglobinopathies to ensure good quality of care. Comprehensive medical care for SCD has significantly decreased morbidity and prolongs life expectancy for patients.[16] The Netherlands has specialised (paediatric) haematologists in all academic centres. Those centres are equipped with a



Multiple sickle cells in a blood smear

dedicated sickle-cell care team consisting of a (paediatric) haematologist, sickle-cell nurse, clinical geneticist, social worker and psychologist, working closely with a variety of sub-specialisms with expertise in SCD (e.g. neurology, cardiology, pulmonology, nephrology, ophthalmology, orthopaedics). This multidisciplinary approach allows for comprehensive, family-centred care for children and adults with SCD. Unfortunately, an extensive analysis of Dutch paediatric SCD patients showed that not all children are provided with such care.[6] This could be due to insufficient access to the Dutch healthcare system by minorities or potential unawareness among health professionals of the importance of comprehensive care for 'less severe' SCD. Regarding the latter, it is of the utmost importance to identify patients and to establish collaborations between paediatricians and haematologists with less expertise on the one hand and specialists in comprehensive care centres on the other, in order to provide the best care possible given current scientific knowledge.

COMPREHENSIVE MEDICAL EVALUATIONS

In summary, all paediatric and adult SCD patients need at least half-yearly scheduled medical evaluations to document baseline physical findings, including blood pressure and peripheral oxygen saturation and the evaluation of growth and development., as well as yearly sampling of blood and urine to detect organ failure. In addition, patients are monitored for complications of SCD including transcranial Doppler (TCD) ultrasonography (due to the high incidence of cerebral infarction [17]) and dilated eye examination (to screen for proliferative retinopathy). If the course of disease is severe or symptoms of deterioration or organ failure occur, treatment is intensified (hydroxyurea, blood- or exchange transfusions) and patients are immediately referred to sub-specialists with SCD expertise. Furthermore, patients and their parents are also followed with regard to quality of life by using validated questionnaires. The results are then integrated in clinical practice to address psychosocial issues in an efficient and effective manner.

SICKLE CELL OUTCOME RESEARCH (SCORE)

The Dutch SCORE consortium was founded in 2016 and is composed of (paediatric) haematologists from seven comprehensive sickle-cell centres (Amsterdam, Rotterdam, Leiden, The Hague, Utrecht, Nijmegen and Groningen). SCORE is designed as a multicentre, prospective cohort study which aims to include the majority of SCD patients in the Netherlands. The goal of the collaboration is to identify factors and biomarkers contributing to the morbidity and mortality of SCD by uniformly collecting data. The research focuses on combining doctor-reported outcome measures (measures assessed by physicians, also called clinical data) with outcome measures from the patients' perspective, also called PROMs (patient reported outcome measures) and PREMs (patient reported experience measures). By incorporating the patients' and families' values, beliefs and cultural norms, the impact of treatment and care can be fully evaluated.

CONCLUSION

Comprehensive care for patients with SCD is a time-intensive endeavour that includes neonatal screening, vaccination and antibiotic prophylaxis, periodic evaluations with screening for complications, and ongoing education of patients and relatives in specialised sickle-cell centres. Nevertheless, even with the best care, many SCD patients still face a lifetime of complications. Methodologically sound research is needed to address evidence gaps and improve our understanding of the best care for these patients. The SCORE initiative hopes to unravel the heterogeneity of the disease and to assess the impact of SCD on the wellbeing of patients and their families.

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Safety of iron supplementation for children in malaria-endemic countries: an unresolved issue

'THE GUIDING SPIRIT [OF INTERNATIONAL EXPERT MEETINGS] IS LED ESSENTIALLY BY THE NUTRITIONAL AGENDA THAT IRON DEFICIENCY IS A COMMON PROBLEM CRYING OUT FOR CORRECTION, AND THAT CLINICAL AND RESEARCH CONCERNS ABOUT THE INTERACTION OF IRON AND INFECTION STRETCHING BACK TO THE 19TH CENTURY ARE NEGATIVE PUBLICITY PROBLEMS TO BE MANAGED RATHER THAN TAKEN SERIOUSLY' – STEPHEN OPPENHEIMER, 2007 [1]

For decades, iron has been routinely given to treat or prevent anaemia in low- and middle-income countries, often in conjunction with folic acid. The World Health Organization (WHO) started advocating universal oral iron supplementation in children in 2001. There have been serious safety concerns, however, about interventions with these micronutrients, and although WHO supplementation guidelines (Table 1) have changed in view of these concerns, they continue to generate controversy and confusion. This paper aims to summarise the key points of that debate. Because of space limitations, I will focus on iron supplementation in children; for folic acid and for iron supplementation in pregnant women, reviews are available elsewhere.[2,3]

EARLY IRON STUDIES AND THE PEMBA TRIAL

There is compelling evidence that the human host provides an environment that limits the availability of iron to pathogens and that increased intake of iron can predispose to pathogenic growth and propagation. Starting in the 1970s, there were reports that iron supplementation leads to an increased risk of malaria, respiratory infections and other infections in developing countries,[4] but these findings were mostly based on observational studies and trials that were relatively small and, at least by modern standards, often had methodological shortcomings. A tipping point came with a large-scale randomised trial conducted among young children in Pemba, Tanzania. This study, published in 2006, showed that daily oral supplementation with iron and folic acid increased the incidence of severe adverse events (hospitalisation and death) by 12% (95% CI: 2%–23%).[5] In 2007, having reviewed the evidence, WHO concluded that the Pemba trial findings were likely due to the effect of iron on malaria. The guidelines were then changed. WHO advised against universal iron supplementation in malaria-

endemic regions, and recommended that iron supplements be administered only in conjunction with measures to prevent and control malaria, and only in children with iron deficiency or, if screening for iron deficiency was impossible, with signs of severe anaemia.[6]

META-ANALYSES OF IRON SUPPLEMENTATION EFFECTS

A subsequent meta-analysis of trials concluded that iron does not increase the risk of malaria or death when regular malaria surveillance and treatment services are provided, and that there is no need to screen for anaemia prior to iron supplementation.[7] This conclusion, however, was mostly based on the risk of malaria. This outcome has low specificity, which may lead to intervention effects being underestimated, and it does not account for possible intervention effects on the severity of malaria.

The results of the Pemba trial suggested that the risks of iron supplementation were restricted to children who were iron-replete at baseline. Iron status was defined by whole blood zinc protoporphyrin content or haemoglobin concentration, indicators that were recently shown to have low diagnostic value for iron deficiency.[8] By contrast, a more recent trial found that supplementation with iron-containing micronutrients increased malaria incidence by 41% (95% CI 9%–82%) in Tanzanian children who were initially iron-deficient,[9] and that this risk declined over the time of intervention. A strong point in the latter study [9] is that, contrary to the Pemba trial, it used a highly specific indicator of iron deficiency (plasma ferritin concentration <12 µg/L). In addition, several studies have shown that iron supplementation in iron-deficient individuals leads to increased erythropoiesis and a transient abundance in circulation of young erythrocytes, which are more susceptible to invasion and propagation by *P. falciparum* merozoites than mature erythrocytes.[e.g. 10] When considered together [9,10], these findings indicate that a screen-and-treat approach is not feasible, because a gain in haemoglobin concentration in iron-deficient children inevitably comes at a price of a transiently elevated risk of malaria.

Subsequent meta-analyses, undertaken by the same group, confirmed the earlier conclusions [8] but emphasised that decisions about iron supplementation should depend on the presence of malaria surveillance and treatment rather than on the assessment of iron status.

CURRENT WHO GUIDELINES REGARDING IRON SUPPLEMENTATION IN CHILDREN

These conclusions are reflected in WHO's most recent guidelines [11], which state that:

a. in malaria-endemic areas, infants and children should be supplemented with iron in conjunction with public health measures to prevent, diagnose and treat malaria;

b. in malaria-endemic areas with limited malaria prevention and clinical care, universal iron supplementation may be associated with an increased risk of malaria;

c. oral iron interventions should not be given to children who do not have access to malaria prevention strategies.

It is plausible and perhaps not surprising that adverse effects associated with malaria are no longer an issue if malaria is adequately controlled. A key problem, however, is that the meta-analyses arbitrarily divided and analysed trials into two groups, depending on whether or not regular malaria prevention or management services were provided, and that this classification may be difficult to translate into practice. For example, the trial by Veenemans et al. [9] provided excellent access to prompt diagnosis and rapid, efficacious chemotherapy, but nonetheless found that supplementation with iron-containing micronutrients increased malaria incidence in children with iron deficiency (see preceding paragraphs). In addition, data on the current state of malaria control, much of which can be found in a recent WHO report [12], is sobering:

a. in areas of stable malaria and under trial conditions, insecticide-impregnated mosquito nets can reduce overall child mortality by only one-sixth and it can only halve the incidence of uncomplicated malarial episodes;

b. only two-thirds of children less than 5 years old in sub-Saharan Africa sleep under insecticide-treated nets, whilst vector resistance to pyrethroids is spreading and intensifying;

c. indoor residual spraying protects only 6% of the population in all of sub-Saharan Africa, with coverage declining in recent years;

d. in 2014, 84% of children under the age of 5 with malaria did not receive appropriate drugs, primarily because a high proportion of children with fever are not taken to a health facility or use the informal private sector.

BACTERIAL INFECTIONS

Most of the debate has focused on malaria, but there is increasing evidence that iron interventions can also increase the susceptibility to both gastrointestinal and systemic infections. Most bacteria scavenge host iron by secreting and resorbing small proteins that bind iron in the environment, by competitively removing iron that is bound to host proteins, by acquiring iron through receptor-mediated uptake of host iron-containing proteins, or by releasing toxins that damage host cells, leading to the release of ferritin, the cellular iron storage protein, or (in case of erythrocytes) haemoglobin. Both iron supplementation and iron fortification can increase the abundance and virulence of enteropathogenic bacteria [e.g. 13], many of which are commonly found in community surveys among children. In an ex vivo study among healthy male volunteers, oral iron supplementation led to a markedly elevated growth of *Escherichia coli*, *Yersinia enterocolitica*, *Salmonella enterica* serovar *Typhimurium*, and *Staphylococcus epidermidis* in sera collected 4 h after intake compared to before taking the tablets.[14] In addition to causing diarrhoea, these infections can lead to bacteraemia, a relatively rare but serious and often fatal condition, and possibly

environmental enteropathy, an asymptomatic but highly prevalent condition among children in developing countries that is marked by increased intestinal permeability, impaired gut immune function, malabsorption, growth faltering, and, potentially, oral vaccine failure.

CONCLUSIONS

In most if not all endemic settings, the coverage and efficacy of malaria control measures remain grossly inadequate, and WHO's current recommendations should not be interpreted as a licence for large-scale iron supplementation programmes in malaria-endemic settings. Further studies are needed to identify antimalarial interventions that can be co-administered so that children receive iron supplementation under the protection of those measures.

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Table 1. Current WHO recommendations on iron supplementation in children

Target group	Policy aim	Recommendations [1]	Reference
Children aged 6 months to 12 years living in settings where the prevalence of anaemia in infants and young children is ≥ 40%	To prevent anaemia and iron deficiency	Daily supplementation for three consecutive months per year, with supplement composition and form as follows: a) 10-12.5 mg elemental iron[2] as drops or syrups (children aged 6-23 months); b) 30 mg elemental iron[2] as drops, syrups or tablets (children aged 24-59 months; or c) 30-60 mg elemental iron[2] as tablets or capsules (children aged 5-12 years)	11
Children aged 24-59 months living in settings where the prevalence of anaemia in infants and young children is 20%-40%	To prevent anaemia and iron deficiency	Consider intermittent regimens of iron supplementation, i.e. weekly supplementation for 3 months, followed by 3 months of no supplementation, after which the provision of supplements should restart, with supplement composition and form as follows: a) 25 mg of elemental iron as drops or syrups (children aged 24-59 months); or b) 45 mg elemental iron, 2 as tablets or capsules (children aged 5-12 years)	11, 15
All children diagnosed with anaemia	To treat anaemia	Follow national guidelines for the treatment of anaemia	11

[1] Oral iron interventions should not be given to children who do not have access to malaria-prevention strategies (e.g. provision of insecticide-treated bed nets and vector-control programmes), prompt diagnosis of malaria illness, and treatment with effective antimalarial drug therapy. See text and original guidelines for other recommendations and conclusions specific to malaria-endemic settings;

[2] 10 mg elemental iron corresponds to 50 mg of ferrous sulphate heptahydrate, 30 mg of ferrous fumarate or 83.3 mg of ferrous gluconate

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Pancytopenia – a common clinical problem that puts a strain on blood transfusion services

CASE

This patient was seen regularly at the internal medicine outpatient clinic of Queen Elizabeth Central Hospital, Blantyre, Malawi.

Female, 22 years, school teacher

PRESENTING COMPLAINT

- Feeling tired

HISTORY OF PRESENTING COMPLAINT

- Multiple visits to clinic and Accident and Emergency Department because of recurrent anaemia
- Was given various courses of iron tablets and albendazole: no improvement
- Needed repeated blood transfusions

PHYSICAL EXAMINATION

- Pale conjunctiva, otherwise normal

INVESTIGATIONS

- Hb 4.9 g/dL (N= 14-16 g/dL)
- MCV 88 fL (N= 76-96 fL)
- TWC 2.1 x 10^9/L (N= 4-10 x 10^9/L)
- Platelets 78 x 10^9/L (N= 150-300 x 10^9/L)

ADDITIONAL INVESTIGATIONS

- Peripheral blood film: normal
- Bone marrow aspiration showed bone marrow aplasia: reduced presence of precursors of all three lineages
- HIV: negative

MANAGEMENT

- Blood transfusions every 6 weeks, for 2 years

She was referred to a hospital in Johannesburg, South Africa, where additional tests were done:

- direct antiglobulin test +ve
- antinuclear factor: +ve, 1: 320, speckled pattern

DIAGNOSIS

Evans syndrome (autoimmune cytopenia), consisting in this case of:

- autoimmune haemolytic anaemia
- idiopathic (autoimmune) thrombocytopenic purpura

In this case possibly associated with Systemic Lupus Erythematosus (SLE) or another autoimmune rheumatic disease.

She was treated with high dose prednisolone and azathioprine that was later tapered to a low maintenance dose with excellent response; no more blood transfusions were needed.

This case of pancytopenia illustrates a common clinical problem that clinicians may encounter everywhere but that in areas with limited resources poses major difficulties. It is difficult to accurately diagnose the underlying condition, and management is often empirical, frequently resulting in repeated blood transfusions.

DEFINITION

Pancytopenia means that all three cell lineages in the peripheral blood (red cells, white cells and platelets) are reduced below the reference range. For each cell line, a reference standard has been published by WHO[1]:

DEFINITION OF PANCYTOPENIA

Cell lineage affected:

- Red blood cells – haemoglobin < 12 g/dL for women; < 13 g/dL for men
- White blood cells - absolute neutrophil count (the majority of leukocytes) < 1.8 x 10^9/L
- Platelets – platelet count < 150 x 10^9/L

PATHOGENESIS

The main (groups of) underlying conditions are listed in Table 1. The most common causes may vary according to the region.[2] Bone marrow aplasia may be the result of damage to the haematopoietic stem cells. Another term that is often used is aplastic anaemia which is actually a misnomer as not only the red cells are affected but also white cells and platelets are involved.[3] Bone marrow aplasia may be caused by virus infections such as HIV or HIV-associated viruses. Drugs are another important cause. Antibiotics such as chloramphenicol are widely used in LMICs and may lead to irreversible bone marrow destruction in 1:20,000-40,000 cases, and there are many more examples of other drugs.[4] Autoimmune antibodies against any of the cell lineages may also occur, and this may also be the case in our patient in the context of SLE.[5]

Alternatively, the bone marrow may not be damaged as such but the cell lines may be displaced by infiltration by a massive infection such as tuberculosis or malignancies such lymphomas. In such cases the bone marrow may recover after treatment of the underlying condition.

The other causes, blood cell destruction and sequestration, are less common, are more difficult to diagnose, and may not easily be recognized in clinical practice. Sequestration of blood cells in a massively enlarged spleen may occur for example in the context of liver cirrhosis and portal hypertension, or in visceral leishmaniasis.[6]

CLINICAL PRESENTATION

The clinical presentation depends on the underlying condition and the resulting anaemia (fatigue, heart failure, ischaemic heart disease), risk of infection (fever, night sweats, yellowing of eyes) and bleeding tendency (bruising, bleeding). Similarly, on examination, lymphadenopathy, hepatomegaly and splenomegaly, jaundice or stigmata of liver disease may be found. There is a long differential diagnosis, and it is useful to distinguish between the main groups. (see Table 1)

DIAGNOSIS

WITH REGARD TO PANCYTOPENIA

In most settings, a full blood count should be possible leading to the diagnosis of pancytopenia as a syndrome. Reticulocyte count is helpful to assess production of red cells; it will be raised in the case of increased peripheral destruction and low in the case of reduced production of red cells in the bone marrow.

A peripheral blood smear may show abnormal cells such as lymphoblasts or myeloblasts in leukemia, or atypical lymphocytes in infectious mononucleosis.

Further analysis should be done at a tertiary referral setting.

A bone aspirate or biopsy would then be the next step and is essential to differentiate between the two main causes: destruction of bone marrow (few haematopoietic cells, empty space filled by fatty cells) and infiltration (e.g. malignant cells in lymphoma, positive Ziehl-Neelsen stain in tuberculosis).[7]

In advanced settings, flow cytometry and other molecular tests would be done to type any abnormal cell to make a firm diagnosis.

WITH REGARD TO UNDERLYING CONDITION

The clinical assessment may provide clues to an underlying condition. Tuberculosis may be suspected in a patient presenting with cough, pleural effusion, ascites or lymphadenopathy; many patients will be HIV positive and an HIV test is always indicated. Diffuse lymphadenopathy with hepato- and splenomegaly may point malignant lymphoma. In addition to clues for a primary tumour, severe weight loss and localized matted lymph nodes may point to malignancy.

Additional tests to diagnose viral infections or to demonstrate autoimmune antibodies or other markers of associated diseases are often not available. Vitamin B12 or folate deficiency may be suspected if the red cells show macrocytosis; in vitamin B12 deficiency, glossitis and subacute combined neuropathy should be looked for.

Depending on the quality of the laboratory, a firm diagnosis may be made, but often the exact cause remains unclear.

MANAGEMENT

In case of an underlying condition, the bone marrow usually recovers with normalization of the cell lineages. In case of bone marrow destruction, e.g. by a viral infection or drug toxicity, damage may be permanent. In addition to recurrent infections and bleeding tendency, recurrent severe anaemia

with a clinical presentation of fatigue, shortness of breath, oedema or overt heart failure is common; repeated blood transfusions are needed that are not always safe and available.

LEARNING POINT

In the case described, it was not possible to make a further diagnosis in Malawi due to a lack of diagnostic capacity. Numerous repeated blood transfusions were given with all their associated risks of infection, fluid overload and transfusion reactions, including dangerous delays in transfusion because of lack of availability. Referral to South Africa in this case was possible. This may be done through a government-funded scheme or at the patient's own initiative. The assessment in the South African hospital revealed a treatable underlying condition in this case that responded well to appropriate therapy and no further blood transfusions were needed.[8] Upgrading of laboratory facilities at least at the central level should be considered to diagnose any treatable underlying condition and to avoid unnecessary life-long blood transfusions.

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Table 1. Causes of pancytopenia according to 4 principal pathological entities

Bone marrow aplasia	Bone marrow infiltration	Blood cell destruction	Sequestration
Infections • HIV • CMV • parvovirus B19 • viral hepatitis	Haematological malignancies • leukaemia • lymphoma • multiple myeloma • myelodysplastic syndromes	Disseminated intravascular coagulation	Hypersplenism • liver cirrhosis • storage diseases • lymphoma • autoimmune disorders
Nutritional • vitamin B12 deficiency • folate deficiency	Metastatic cancer	Thrombotic thrombocytopenic purpura	
Immune destruction • autoantibodies	Myelofibrosis		
Medication • antibiotics e. g. chloramphenicol • NSAIDs e.g. ibuprofen • Anti-epileptics	Infectious diseases • tuberculosis • fungal infections		

On October 28, 2017, the NVTG – in collaboration with Uniting Streams and TROIE – organised the first Dutch Global Health Film Festival in Filmtheater 't Hoogt, Utrecht.

Global health and cinema: a great combination

A review of the first Dutch Global Health Film Festival

The face of a Ugandan woman fills the screen, her lively smile revealing a missing front tooth. I am at the first Dutch Global Health Film Festival and not the only one. Tickets have sold out quickly and the cinema is crowded with students and health professionals, all sharing an interest in global health. The program includes three sessions with films and panel discussions with experts in the field.

As the first film continues, we learn that the woman's name is Hellen Baleke. She lost her tooth during one of her fights, as she is one of the few female boxers in the country. She started boxing as a means of self-defence in the slums of Kampala but now only fights inside the ring. And with success: if women received medals for the fights they won, like their male counterparts, she would have had plenty by now. For Hellen, boxing is about more than winning medals alone. Her fight is also for gender equality in this popular sport in Uganda. And with success, as director Chrisje Sterk tells us after the viewing of the film. Together with her sister Diana, she was the first woman to represent Uganda during the 2014 Women's World Boxing Championships. The fact that she almost set a world record in giving up – in one of her fights she threw in the towel after 11 seconds – is not important. She has won my respect.

'The Checklist effect' is a documentary on surgical needs worldwide. In a journey around the world, we see how surgical treatments can be improved. The needs are diverse, such as in Guatemala where we see the effects of malfunctioning surgical equipment. The surgical team is not able to sterilize surgical instruments because of power-cuts, and a patient with pulmonary embolus dies because of a lack of post-operative monitoring and a broken alarm system. The documentary is largely based on the book by surgeon Atul Gawande on the development of the WHO Surgical Safety Checklist. We see how a peri-operative checklist is used in the US to improve communication among different members of the surgical and anaesthetic team, thereby improving patient safety. And in Mongolia, where surgical training lasts only 3 months (!), training programs are implemented to improve the quality of care. The importance of safe surgery and anaesthetic care is illustrated in the closing credits, where we learn that almost half of the film's casting team and crew have checkmarks behind their names, indicating that they underwent surgery at some point during their lives.

The impressive 'Minutes to die' documentary discusses a neglected tropical health issue, the snake bite. We see several victims of snake bites, such as an African family which lost its first child due to a snake that also severely physically disabled their second child and an Indian father in life-threatening condition after being bitten by a snake. Dr David Williams, present during the discussion after the film, is a strong advocate of focusing more attention on the devastating effects of snake bites. He explains that even though we can't eliminate snakes, as they are an important part of our ecosystem, we can create more awareness to prevent snake bites. Also, we should invest in the production of anti-venom, which at present is either not available, not efficient, or too expensive. The documentary shows how his protracted lobbying efforts for the inclusion of snakebite envenoming in the WHO list of Neglected Tropical Diseases finally paid off in 2017.

'The Great Escape' is a short film produced by The Joep Lange institute. It shows the role of technology in pursuing equity and portrays the cell phone as being 'the biggest equalizer'. We see a young Kenyan woman, mother of 5 children and HIV positive. She struggles to take care of her family. To be able to pay for her hospital check-ups and treatment, she uses M-tiba, her phone wallet, which keeps her from spending money on other things. As she puts it, 'If it were not for the wallet, I would not be alive'.

The film 'Breaking the chains' shows the heart-warming dedication of a local Indonesian team whose mission is to free mentally ill people who are held in 'pasung', the local term for the (illegal) practice of physical restraint and confinement. Their illness being misinterpreted as possession by a 'jinn', they are neglected and kept from society in a small hut or shed, sometimes for years on end. Local health workers team up with people who suffered from mental health disorders themselves and visit the patients, many of them hidden in extreme circumstances in remote rural areas. They offer treatment and compassion and try to convince their families to literally break their chains, sometimes with success, although poor adherence to medication and relapse make the job difficult and time-consuming. After the film, director Dr. Erminia Colucci tells us she will be going back to Indonesia to follow up on the people featured in the documentary, so hopefully we can expect a sequel soon. Credits to the organizers of the film festival for their selection of impressive documentaries and facilitation of inspiring discussions. Looking forward to the next edition!

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Supplying safe blood: the Malawi experience

Collection of blood from regular voluntary non-remunerated blood donors is one of the key strategies for blood safety promoted by the World Health Organization (WHO).[1] The Malawi Ministry of Health adopted this strategy and established the Malawi Blood Transfusion Service (MBTS) in 2004 as an independent nationally coordinated blood transfusion service based on voluntary non-remunerated blood donation.[2] Blood collections have increased 12 fold in 12 years from 5000 in 2004 to 60,000 in 2016 (Figure 1). This is commendable progress considering that promoting voluntary unpaid blood donation started during a time when Malawi was awash with myths and rumours of blood suckers. However, these collections still fall short of the 120,000 national blood collections needed by about half and constitute about 64% of all blood that is collected nationally, highlighting a chronic national blood shortage.[3] The remaining 36% of blood transfusions are emergency donations in hospitals.

This article aims to share the Malawi experience in supplying safe blood. It describes the country, the Malawi Blood Transfusion Service, some successes, and the challenges that still remain.

Malawi is a densely populated Southern African country with a 2016 estimated population of 17.1 million, 84% of whom live in rural areas.[4] Life expectancy at birth was estimated at 63.9 for both sexes in 2017].[5] Malawi's 2015 Gross Domestic Product (GDP) was USD 381.40 per capita.[6] The economy is predominantly agro-based.[7] In 2016, the maternal mortality ratio was 439/100,000 live births and the under-five mortality rate was 63/1000. HIV prevalence was 8.8% in men and women aged 15-49 years while the national prevalence of hepatitis B and hepatitis C is unknown.[8]

The Government of Malawi (GoM) provides healthcare to 70% of the population, the Christian Health Association of Malawi (CHAM) to 29%, and the remainder is provided by private hospitals and non-governmental organizations (NGOs).[9] Services provided by GoM institutions do not charge user fees while CHAM and NGOs charge subsidized fees and private facilities charge market-based fees. There are four tiers of health service provision, namely those responsible for provision of community, primary level, secondary level, and tertiary level services. Blood transfusion services are provided at secondary and tertiary level health care facilities. In total, there are 88 such facilities nationally.[9]

ESTABLISHMENT OF THE MALAWI BLOOD TRANSFUSION SERVICE

The Malawi Blood Transfusion Service (MBTS) was established by the Ministry of Health in 2004 as an independent nationally coordinated blood transfusion service based on voluntary non-remunerated blood donation. It is registered as a welfare trust with a board of trustees that is appointed by the Minister of Health of Malawi. Of its four centres, two are located in the southern region and one each in the central and northern regions. The headquarters is in Blantyre, Southern Region. All centres are responsible for blood collection and blood distribution. Three of the four centres also make blood components as follows: adult and paediatric red cell suspensions, fresh frozen plasma, cryoprecipitate, and platelet concentrates. Some blood is issued as whole blood.

SCREENING

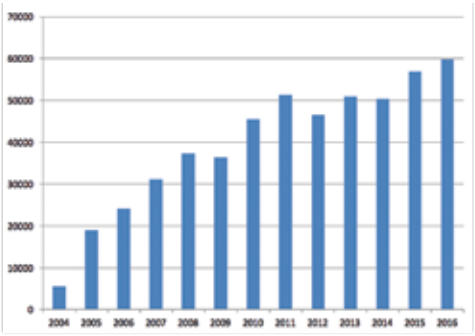
Donated blood is screened for HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), syphilis and malaria. The following markers are screened for using enzyme immunoassays: HIV (antibodies to HIV I & II and p24 antigen); HBV (HBsAg); HCV (anti-HCV antibodies). The Treponema Pallidum Haemagglutination Assay (TPHA) is used for syphilis screening while thick film microscopy is used for malaria screening. The seroprevalence for HIV, HBV, HCV and syphilis in the blood donor population has decreased between 2011 and 2015 (where comprehensive data is available). The seroprevalence for 2011 and 2015, respectively, was: HIV 3.5% and 1.9%; HBV 4.7% and 3.5%; HCV 2.4% and 1%, syphilis 3.2% and 2.3%.[10]

The prevalence of malaria in 2015 was 0.9% (unknown for 2011). The test kits and algorithm remained the same over this period. Testing is centralized and takes place at the headquarters in Blantyre (Figure 2).

COLLECTION OF BLOOD

Blood is collected from all communities across Malawi, which include schools, colleges, workplaces, places of worship and markets. Since 2015, a new initiative was introduced to target the large rural population by collecting blood from villages (Figure 3). In all these communities, blood donation is preceded

Figure 1 Number of blood collections since establishment of the MBTS



by a motivational talk which educates blood donors about blood donation but also motivates them to become blood donors. There are also radio and television adverts and programs on blood donation. Regular blood donors are recognized with milestone awards such as T-shirts, head caps, certificates and golf shirts depending on the number of donations made, with golf shirts being given to those who have made at least 25 blood donations. There is also the Blood Donor Association of Malawi (BDAM) and its youth wing the Malawi Club 25. The Chairperson of BDAM is an ex-officio member of the Board of Trustees of the MBTS. Club 25 members are enrolled when they are between 16 and 25 years old. They pledge to donate at least 25 blood units in their lifetime.

On average, about 40,000 [2011-2015 range of 37,111-41,728] people donate blood each year. The blood donor population is young [median age of 19 years; range 16-65 years], and 80% are 25 years or younger. Amongst all blood donors, 72% are students, 87% are not married and 80% are male.[10] Young males in Malawi have the lowest prevalence of HIV (1% for males aged 15-24 years compared to 4.9% for girls of the same age group and a national average of 8.8% for adults 15-49 years old).[11] Repeat blood donation rates have been declining from 58% in 2011 to 51% in 2015. The reason for this is unclear.[10] The low number of people donating blood, the declining proportion of repeat blood donors, and the reliance on young student blood donors are some of the challenges that contribute to not meeting annual blood needs and severe blood shortages during school holidays. Female blood donors have half the hepatitis B risk of male blood donors (adjusted odds ratio 0.51, CI 0.43-0.60); for males, traditional circumcision and shaving in barbershops are thought to possibly play a role here.[10] As hepatitis B has the highest prevalence in the blood donor population of all diseases screened for, understanding the factors responsible for the high risk of hepatitis B in males can help devise interventions that protect the predominantly young male blood donor population from acquiring hepatitis B and thereby help sustain increased blood donation levels in this population. Hopefully, the universal vaccination for HBV that started in 2005 will have a major impact over time.

FUNDING

The MBTS was initially established with a 9.36 million euro grant from the European Union. This grant came to an end in 2006. Unlike other cases where projects were not sustained beyond project funding, MBTS continued to not only exist after this funding stopped but actually expanded its operations from collecting about 24,000 units of blood in 2006 to more than double that amount within 10 years. Further funding comes from the Global Fund to Fight Tuberculosis, AIDS and Malaria (GFTAM), the Presidential Emergency Plan for AIDS Relief (PEPFAR) through the Centres for Disease Control and Prevention (CDC), and from a cost recovery mechanism where hospitals are billed for blood units supplied. Cost recovery in the health sector started in 2007 with private hospitals only and was later expanded to cover all hospitals from 2009. By 2016, cost recovery was funding 54% of the USD 3.14 million MTBS annual budget, while the contribution by PEPFAR was 29% and GFTAM 17%. The dependence on external support is still significant and poses a risk to the sustainability of the blood services.

CONCLUSION

It is possible to improve the microbiological safety of the national blood supply and to provide blood through a centralized national blood service in a developing country. A high burden of hepatitis in the young male population who seem to have selected themselves for blood donation based on their low risk for HIV needs to be addressed. Reliance on external funding, a young blood donor population, and low blood donation per capita remain challenges that need to be addressed to improve accessibility to safe blood supplies.

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Insights into Burkitt lymphoma

This overview was compiled after a discussion between Trijn Israels as an expert in the subject and Ed Zijlstra on behalf of the Editorial Board of MT.

SHORT CV

Trijn Israels (51) is a Dutch paediatrician who trained in the Academic Medical Center, Amsterdam, with further specialization in paediatric oncology. She worked in Malawi in 2003 and from 2006-2008 in the Department of Paediatrics of the College of Medicine and Queen Elizabeth Central Hospital, Blantyre, with special interest in childhood oncology. Her PhD thesis (2010) was titled 'Aspects of management of children with cancer in Malawi'. She has been co-chair of the Committee of Paediatric Oncology in Developing Countries (PODC) of the International Society of Paediatric Oncology (SIOP) and is now coordinator of the Collaborative Wilms Tumour Africa Project which is implementing an adapted treatment guideline for Wilms tumour in eight centres in five countries in sub-Saharan Africa. Currently she is working as a paediatrician in the Amphia Hospital in Breda, the Netherlands.

This paper describes Burkitt lymphoma in a resource-limited setting, in particular in Malawi.

INTRODUCTION

Burkitt lymphoma (BL) is a unique tumour; it is has the highest cell replication rate of all human malignancies with a cell doubling rate of 24-48 hours. This causes rapid clinical progression and also makes it amenable to effective cytostatic therapy that interferes with the cell replication mechanism.

There are three types of BL of which the endemic form (eBL) is the most important. It is also the most common tumour during childhood in areas where malaria is endemic, a relationship described in 1958 by Denis Burkitt, an Irish surgeon who worked in Uganda. At around the same time, Epstein Barr Virus (EBV) particles were detected in lymphoma tumour cells. Although the exact mechanism is unknown, BL is thought to be caused as the result of interaction between EBV and the malaria parasite. As EBV infection and malaria both are common in young children, BL is mostly seen in young children between 4 and 9 years of age; boys are twice as frequently affected as girls.

The sporadic variant of BL (the second type) occurs in Europa and North America; here the relationship with EBV is less clear. The third type is the immune-deficiency related BL that was commonly seen in HIV infected individuals before the introduction of antiretroviral therapy, in particular early in the progression of the disease.

CLINICAL PRESENTATION

The most common localizations are in the eye, jaw and abdomen. The first two give the typical presentations of eBL with eye protrusion and periorbital swelling, and swelling of the jaw (Figure). In addition, the child may present with abdominal BL resulting in rapid swelling of the abdomen with ascites. The child is typically (severely) malnourished because of the metabolic demands of the rapidly growing tumour (Figure). Less common is localization in the central nervous system. In the brain, eBL leads to confusion, visual loss, and reduced consciousness and may be fatal. A BL mass may also compress the spinal cord leading to paraplegia and bladder incontinence. In Malawi, the majority of children present with some form of facial disease and many of them also have abdominal disease.

Many patients present at the clinic with advanced stage of disease. Sources of delay in diagnosis and treatment are many. These include primary consultation of a traditional healer (who may apply scarification), limited knowledge among health workers of the disease and treatment options, and barriers in referral and access to central hospitals. Clearly any delay in treatment allows the tumour to grow resulting in more severe disease with negative consequences for the response to treatment; this is particularly so in children with severe wasting. In Malawi, eBL is treated in two central hospitals in Blantyre and Lilongwe. The referral rate has increased in recent years, reflecting greater awareness of the disease and better options for treatment.

BL is diagnosed by a fine needle aspiration of the lesions; staging to describe the extent of the disease includes a bone marrow aspirate and examination of the cerebrospinal fluid for malignant cells.

The treatment of eBL in Malawi and other centres in sub-Saharan Africa has improved considerably in recent years. The simplest, standard treatment regimen includes a 28 day treatment schedule with cyclofosfamide, first IV on day 1, then oral on days 8, 18 and 28, with intrathecal administration of

methotrexate and steroids to prevent relapses from untreated lymphoma foci in the brain. With this regimen, a 50% cure rate can be achieved; in those who relapse, repeated courses of second-line treatment are given with cure in another 15%. In those not responding, the prognosis is poor. The cost of drugs is around USD 50.

Over the years, studies have been done to further improve the cure rates. Adding vincristine to first-line treatment and using high methotrexate dosages proved not effective or was too toxic. Another study led to better outcome in severely malnourished children by adapting the dosage to reduce side-effects. Staging has become the norm; those with extensive disease receive higher doses of drug with better survival rates, although with more toxicity. The latest very promising approach is with a monoclonal antibody (rituximab) that specifically targets the tumour cells, with very little toxicity. It is currently expensive (around USD 1000 per patient treated with a full dose); studies are ongoing.

THE FUTURE

The understanding of the biological behaviour of eBL and its management have considerably improved over the years. International collaboration, both regional and with partners in high-income countries (HICs), has increased through successful twinning with a collaborating centre. World Child Cancer, which funds childhood cancer projects in low-income countries, was founded about a decade ago. Pragmatic, adapted treatment guidelines for the most common and curable childhood cancers such as retinoblastoma, eBL, Kaposi's sarcoma, and Wilms tumour have been published by the International Society for Paediatric Oncology (please see further reading below).

Several lessons have been learned for a better approach to eBL treatment in a resource-poor setting. First, emphasis should be on completing the treatment course, as most failures result from premature stopping of treatment or defaulting. While this was common in the past, improved clinical management, with less side-effects of drugs, and counselling have led to much improved compliance.

Second, compared to high-income countries, the treatment should be of low intensity to avoid toxicity related deaths. Lastly, to realize optimum results, taking these two issues into account, study protocols should be developed locally and not copied from HICs.

In conclusion, important progress has been made in the treatment and outcome of this common childhood tumour in resource-limited settings.

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Two patients with endemic Burkitt Lymphoma in the abdomen and on the jaw

FURTHER READING

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COLOPHON

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Managing thrombosed haemorrhoids – not as straightforward as it seems

SETTING

This case is from Kikori District Hospital in the remote Gulf province of Papua New Guinea (PNG). This district hospital has 80 beds and very limited diagnostic tools. There is no access to laboratory tests other than tests for HIV, syphilis, tuberculosis and malaria. Ultrasound is available. Due to its location amid the jungle, referral is only possible for rich people. In case of a life-threatening (surgical) emergency and good weather, an evacuation by helicopter is possible.

CASE

A 25-year old woman presented to the outpatient clinic with severe rectal pain since several days. She had been suffering from haemorrhoids for years, mostly resulting in mechanical problems and occasional rectal bleeding. She also reported regular protrusion of the haemorrhoids, requiring manual reduction. The precipitating factor was constipation. She had never been treated for haemorrhoids before. Her medical history was otherwise unremarkable with no use of medication. On physical examination, a bluish-purple tumour was seen protruding from the anus, which was firm and very painful on palaption. There was no rectal bleeding.

The diagnosis of a thrombosed external haemorrhoid (TEH) was quickly made. The problem, however, was the treatment, as literature discussing the preferred treatment was contradictive. Some sources advised surgical treatment, as this would offer immediate relief of pain. Other sources favored a conservative approach, which was thought to be equally effective with the added benefit of avoiding surgical complications.

SPECIALIST ADVICE

Due to this conflicting information, Dutch surgeons were consulted on the preferred treatment for this patient. The tropical doctor mentioned that her personal preference would be to avoid surgical treatment due to the limitations in the provision of anaesthesia in the hospital.

Within a few hours, three surgeons had replied to this query. Their opinions were a good representation of the literature; there did not seem to be a gold standard for treatment of a TEH. One of the surgeons preferred surgical treatment under pethidine and diazepam, arguing that this would give increased patient satisfaction. Merely rinsing the area with water would be sufficient postoperative treatment. The other two surgeons had a preference for conservative treatment. They argued that systemic or local anaesthesia would suffice to reduce the pain, while surgical treatment could give rise to complications such as bleeding, increased pain and damage to adjacent tissue. Furthermore, they warned that surgical excision might not be as easy as it seems, as the swollen tissue would make it difficult to recognize the anatomy. Conservative treatment could consist of topical and oral lidocaine, wet compresses or ice packs, and laxatives.

FOLLOW-UP

Following the specialist advice, the patient was treated conservatively with ice packs, lidocaine gel, bisacodyl and pethidine injections. The ice packs were most effective in reducing the pain and swelling. After a few days, the haemorrhoid decreased in size. The patient was discharged after two weeks. By that time, she was pain free with only a small residual swelling. The patient has not been back to the hospital since.

BACKGROUND ON THERAPY

CONSERVATIVE TREATMENT

The conservative treatment of TEH consists of symptomatic treatment (analgesics), preventative treatment (changes in diet, stool softeners) and curative treatment (local applications to quicken spontaneous resolution, which normally takes three to four weeks).[1] A more recent addition is topical nifedipine, which reduces pain and time to resolution.[1]

SURGICAL TREATMENT

Commonly, surgical treatment is done when conservative treatment fails.[1] There are different surgical techniques, including excision of the haemorrhoid or incision and drainage. Incision is used less by surgeons due to the possibility of persistent bleeding and more recurrence[2]; excision is therefore preferred.

In an article comparing the conservative and surgical treatments, the latter was better in terms of symptom resolution (occurring after 4 days instead of after 24), recurrence rate (6% versus 25%), and time to recurrence (25 months instead of 7 months after initial treatment).[2] The surgical treatment consisted of incision and drainage in 3% of cases, while excision of the thrombosis and vessel was done in 97%.

One of the advising surgeons provided his expert opinion about the surgical treatment (Box 1).

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BOX 1: THE SURGICAL TREATMENT OF THE THROMBOSED EXTERNAL HAEMORRHOID IN A LOW-INCOME SETTING

A thrombosed external haemorrhoid (TEH) is an acute and very painful condition. Instead of initiating a treatment based merely on protocols and guidelines, it is important to take into account the circumstances in which a patient lives. For example, a patient with a TEH living in primitive circumstances, like the woman in this case report, might require different treatment than our Dutch protocols dictate.

TREATMENT

A TEH is often managed conservatively. This is appropriate for patients with comfortable living conditions like ours, with access to optimal health care, appropriate dressings and bandages, running water and hygienic toiletry facilities. However, people living in primitive circumstances are better managed surgically. Incising and removing the thrombus yields an immediate and thankful result. The follow-up care is less intensive than with conservative treatment and medication is hardly necessary.

TECHNIQUE

The patient is positioned on his side, with the knees pulled up towards the chest. After applying local anaesthesia (lidocaine 1%, if possible with adrenaline) around the haemorrhoid, an incision is made on the central point of the thrombus. In most cases, this will lead to spontaneous expulsion of the thrombus. Any remaining thrombus can be removed with a gauze. To prevent postoperative bleeding, a vaseline-coated gauze can be placed partially in the wound and partially in the anus. The patient is required to rinse the anal area with water several times a day. A laxative diet is advised.

COMPLICATIONS

There are hardly any complications after this procedure. Sometimes the patient will have a little blood loss during a few days. Infection is almost never seen when the perianal region is frequently cleaned by "watering" this area. Also, there will be no incontinence.

ADVANTAGES IN A LOW-INCOME SETTING

The advantages of surgical treatment are clear:

- easy intervention with satisfactory results for the doctor
- quick treatment and immediate pain relief for the patient
- simple maintenance care, even in primitive circumstances

CONCLUSION

When practicing medicine in low-income countries, occasionally a different treatment should be applied than in high-resource settings. In case of a TEH, incision and removal of the thrombus is both easy and effective.

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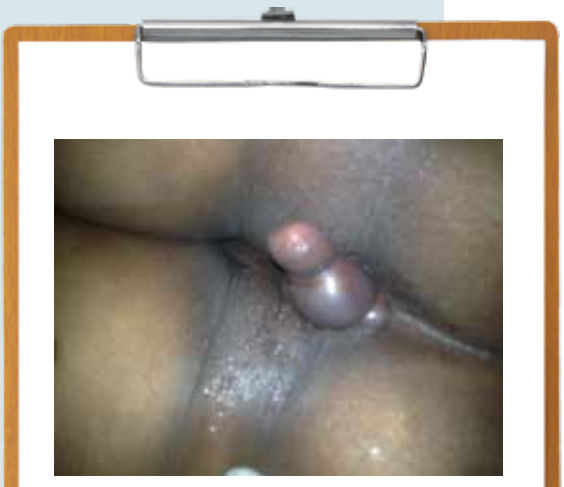
DR H.F. VEEN
SURGEON IN RETIREMENT



A bluish-purple tumour is protruding from the anus.

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INTO THE WORLD - EXPERIENCES AND VIEWS OF MEDICAL DOCTORS GLOBAL HEALTH AND TROPICAL MEDICINE

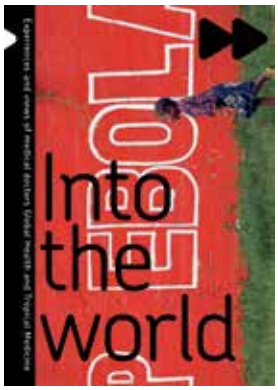
Written by **Marlies Hummelen et al.**
Edited by **Matthijs Botman**
204 p., hard-cover. English or Dutch.
Price EURO 28,50.

Into the world is available through www.boekschap.nl or www.artsinternationalegezondheidszorg.nl

An intriguing title, an intriguing book - *Into the world* takes the reader on a journey into the world of those formerly known as 'tropical doctors'. The new name, 'medical doctor Global Health and Tropical Medicine' (AIGT) is perhaps less catchy, but it better represents what this type of doctor stands for. In twelve interviews with such doctors, all with a different backgrounds and career paths, we learn about the diverse facets of their role in the global health field - then and now, here and there. André Veneman still feels like a 'tropical doctor' even now in his current position as corporate director Sustainability for AkzoNobel, many years after he started his career as a young doctor in a refugee camp in Thailand in the 1980s. Erna Rijnierse also works with refugees in her function as medical doctor in the emergency team of MSF. She deals with 'modern day' refugees. After several decades, the needs are still there. Or are they? To a certain extent, yes, though perhaps varying in form and scope.

Take for example Namibia, where the country is welcoming its first batch of Namibian trained medical doctors. For Steffie Heemelaar – an AIGT working in Namibia and doing PhD research – this is a valid question. And the answer is not clear-cut, as this book aptly illustrates. Others also reflect on the new role of MD GH and TM, like Marijke Wijnroks – once a young doctor working for MSF in South Sudan who made a career in international health diplomacy. 'We should be investing in capacity building for doctors in low- and middle-income countries'. But hands-on experience is very valuable, especially in the field of global health policies. A common thread in all the stories here is the added value of the experience abroad. For some, the years abroad helped shape their focus in the Netherlands. These years also helped make participants more critical of their own health system. Albertine Baauw – former tropical doctor, now paediatrician – points to the irrational choices we make in the Netherlands such as not including standard screening for immigrant children arriving here from epidemiological hotspots.

Besides the 12 interviews, *Into the world* also invited 5 health professionals and experts from outside the Netherlands to share their experiences in working with Dutch medical doctors in the field, or to reflect on current issues in global health like the human resources for health dilemmas. Richard Smith – chair of ICDDR,b (formerly International Centre for Diarrhoeal Disease Research, Bangladesh) – summarises it by saying 'It's time for the North to learn from the South'. He underlines the vision of Lord Crisp (former chief of the UK NHS) in his book *Turning the world upside down*, 'Health care workers from high-income countries who spend time working in low-income countries may learn much that will benefit health systems in high-income countries. In addition, they develop a set of attitudes and skills that are useful anywhere.'



The book is an enjoyable, thought-provoking and above all inspiring read.

Some years ago, a medical student asked Matthijs Botman – the initiator of the book and of the campaign seeking sustainable funding for the accredited training programme – a question. Should he pursue becoming a 'tropical doctor'? During my days as chair of the NVTG, advocating for quality education for MD GHTM in the Netherlands, we reflected quite extensively on many of the issues this book is dealing with. Rowing against the prevailing current, the NVTG continued to believe in the value of having well trained doctors to fill a gap and build capacity worldwide as well as to strengthen our own health care system. Was it worth it? Judge for yourself by reading this book.

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THE BEAUTY OF THIS BOOK IS THAT IT HELPS US REFLECT ON OUR ROLE AS HEALTH PROFESSIONALS IN A GLOBALISED WORLD. IS IT STILL WORTHWHILE TO KEEP SENDING OUR HEALTH WORKERS ABROAD?

Dreaming out loud!

Dear readers of MT, dear members of the NVTG,

In 2017 we celebrated our 110th anniversary with a series of events including our annual symposium, a film festival, a book launch, meetings and symposia organized by different working groups as well as meetings with our members and partners on various other occasions in the Netherlands and abroad. We thank you for these encounters and your continued support in the shaping of our Society.

We are about to close the 2017 chapter, looking back at an eventful year filled with good memories. Those who attended our symposium in June on *110 years of International Health and Tropical Medicine* may remember how Leo van Bergen placed us in front of the mirror and reflected on how the NVTG has dealt with changing realities, challenges and opportunities over the years. The world definitely has changed, though listening to his words one might conclude that some things did not change. As in the early days, the NVTG remains a space for scientists, researchers and policy makers to meet and to discuss current matters in the wide field of international health and tropical medicine and to share ideas and experiences.

Still going strong at 110, we take this opportunity to dream about our future. Our dreams are realistic enough to be realized, certainly with the wide network of active members and other allies who have been working with us throughout all these years. We would like to share our dreams here as well as the actions needed to realise them:

- **Embracing diversity.** Global health flourishes through the engagement of professionals from different backgrounds. Over the decades, the NVTG has evolved from a society with predominantly medical doctors to the society we are now, with a variety of members from different disciplines including sociologists, health scientists, epidemiologists, nurses, paramedics etc. We are realizing our dream of opening the doors of our society to all professionals interested in global health, while at the same time continuing as a professional association for Medical Doctors in Global Health and Tropical Medicine.
- **Positioning global health in the Netherlands.** The NVTG is the home base for professionals who are used to working in health systems abroad, working with clients from different cultures, and dealing with tropical diseases. The art of dealing with these challenges is a valuable asset in the Dutch health (care) system. The testimonies and reflections compiled in the book *Into the World* describe the experiences these professionals went through and where they are now. We will, of course, continue to do our best to realize sustainable financing mechanisms for the training programme to become a Medical Doctor Global Health and Tropical Medicine.
- **Stimulating cross fertilisation.** We continue to bring together experts and expertise in global health including clinicians, public health specialists, researchers in tropical medicine, and health systems analysts. We continue to look further afield and to attract new young professionals to the Society. At the same time, we are also exploring new funding opportunities such as those channelled through the Otto Kranendonk Fund, which enables young researchers at the beginning of their career to do research.
- **Providing a platform.** Technological innovations enable NVTG to embrace new ways of communicating. Physical meetings will still be at the core of our work, but we will also invest in other ways of meeting and communicating through our new website (upcoming) and social media.

We wish you a peaceful Christmas and a wonderful 2018.

The NVTG Board

NVTG

Membership of the **Netherlands Society for Tropical Medicine and International Health** (NVTG) runs from January 1st to December 31st and may commence at any time. Membership will be renewed automatically unless cancelled in writing before December 1st. Membership includes MT*b* and International Health Alerts. An optional subscription to TM&IH carries an additional cost. Non NVTG members can subscribe to MT*b* through a student membership of the Society for€ 40 per year by sending the registration form through our website www.nvtg.org/lidworden.php or by sending name and postal address by e-mail to info@nvtg.org or MTredactie@nvtg.org. Contributions and announcements should be submitted to the editorial office by e-mail: **info@nvtg.org** or **MTredactie@nvtg.org**. Closing date for the March issue is 12-01-2018.

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