Online Submissions: wjg.wjgnet.com
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doi:10.3748/wjg.15.2839

World J Gastroenterol 2009 June 21; 15(23): 2839-2854
World Journal of Gastroenterology ISSN 1007-9327
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TOPIC HIGHLIGHT

Dr. Shahid A Khan, *Series Editor*

Gastroenterology in developing countries: Issues and advances

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Author contributions: Mandeville KL and Khan SA developed the structure of the paper; Mandeville KL wrote the manuscript; Quigley EMM, Mulder CJJ, Krabshuis J, Ladep NG and Khan SA contributed sections to the paper and reviewed the manuscript.
Supported by The NIHR Biomedical Research Centre funding scheme, the Higher Education Funding Council for England (HEFCE), the British Liver Trust and the Alan Morement Memorial Fund AMMF, Essex, UK
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Received: February 3, 2009 Revised: April 21, 2009
Accepted: April 28, 2009
Published online: June 21, 2009

Abstract

Developing countries shoulder a considerable burden of gastroenterological disease. Infectious diseases in particular cause enormous morbidity and mortality. Diseases which afflict both western and developing countries are often seen in more florid forms in poorer countries. Innovative techniques continuously improve and update gastroenterological practice. However, advances in diagnosis and treatment which are commonplace in the West, have yet to reach many developing countries. Clinical guidelines, based on these advances and collated in resource-rich environments, lose their relevance outside these settings. In this two-part review, we first highlight the global burden of gastroenterological disease in three major areas: diarrhoeal diseases, hepatitis B, and *Helicobacter pylori*. Recent progress in their management is explored, with consideration of future solutions. The second part of the review focuses on the delivery of clinical services in developing countries. Inadequate numbers of healthcare workers hamper efforts to combat gastroenterological disease. Reasons for this shortage are examined, along with possibilities for increased specialist training. Endoscopy services, the mainstay of gastroenterology in the West, are in their infancy in many developing countries. The challenges faced by those setting up a service are illustrated by the example of a Nigerian endoscopy unit. Finally, we highlight the limited scope of many clinical guidelines produced in western countries. Guidelines which take account of resource limitations in the form of "cascades" are advocated in order to make these guidelines truly global. Recognition of the different working conditions facing practitioners worldwide is an important step towards narrowing the gap between gastroenterology in rich and poor countries.

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Key words: *Helicobacter pylori*; Developing countries; Gastrointestinal diseases; Health care delivery; Practice guidelines

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Mandeville KL, Krabshuis J, Ladep NG, Mulder CJJ, Quigley EMM, Khan SA. Gastroenterology in developing countries: Issues and advances. *World J Gastroenterol* 2009; 15(23): 2839-2854 Available from: URL: http://www.wjgnet.com/1007-9327/15/2839.asp DOI: http://dx.doi.org/10.3748/wjg.15.2839

INTRODUCTION

Despite political rhetoric, foreign aid, and increased global wealth, the disparity between the developing and developed world is more evident than ever before.

Recently, the economic successes of China and India have lessened poverty for millions of people. Nevertheless, these countries aside, international inequality in income has continued to rise over the past two decades[1].

Nowhere is this inequality clearer than in the arena of health. A child born in Angola in 2006 has a 26% chance of dying before its fifth birthday. In the UK, that risk is 0.6%. In 2006, the life expectancy for a woman from the United States of America was 80 years. If she was instead living in Zambia, her life expectancy declines to just 43 years[2].

In this review, we examine some of the main challenges in developing countries, and discuss potential and existing solutions. Our definition of developing countries is that set out by the International Monetary Fund; "countries with low levels of output, living standards, and technology; per capita GDPs are generally below $5000 and often less than $1500"[3]. The converse, developed countries, will be referred to as "western countries" for clarity. In common practice, these include most of Europe, North America, Japan and Australasia[3] (Figure 1).

The focus of the review will be on gastroenterological problems which head the global disease burden. Although challenges such as war, inadequate water and sanitation, and economic failure all undoubtedly impact on global health, it is beyond the scope of this article to discuss these factors in detail. Moreover, whilst problems such as unstable governments, sectarian violence, and environmental catastrophe undeniably compound health issues, they are by no means confined to developing countries.

In the first part of this review, we will focus on three significant areas of gastroenterological disease which highlight particular problems in developing countries: diarrhoea, hepatitis B and *Helicobacter pylori* (*H pylori*).

The second part of the review will consider the implementation of clinical services in developing nations, encompassing the health workforce, endoscopy services, and the relevance of resource-blind guidelines.

GASTROENTEROLOGICAL DISEASE BURDEN OF DEVELOPING COUNTRIES

Diarrhoeal diseases

The global burden of diarrhoeal diseases outweighs any of the more complex diseases seen in gastroenterology clinics. Every year, there are an estimated 1.5 billion episodes of diarrhoea worldwide[4]. These episodes result in the deaths of approximately 2.2 million people, mostly children in developing countries[4]. This mortality rate has improved from the early 1980s, when diarrhoea is estimated to have caused 4.5 million deaths in children alone[5]. However, it is still the third leading cause of death in under-5 years old, after neonatal causes and pneumonias[6].

Developing countries bear the brunt of this burden. Diarrhoea causes 17.9% of deaths in low-income countries compared to 1.6% in high income countries[6]. Most of these cases are due to the lack of safe water, sanitation and hygiene. Only 34% of people in low-income countries have access to adequate sanitation[6]. As mortality rates from diarrhoea are now so low in western countries, the scale of disease is often expressed in terms of financial costs instead: hospitalisation rates and doctors' consultation time[7]. However, these can be overused resources in the West, and are thus poor comparison measures between countries.

Figure 1 Distribution of countries as per International Monetary Fund (IMF) definitions of economic development (IMF statistical database[3]: reproduced with kind permission of IMF).

Diarrhoeal diseases are caused by a wide variety of pathogens. In 1991, the World Health Organization (WHO) performed a case-control study of the aetiology of diarrhoea in children under 36 mo of age, in five countries: China, India, Mexico, Myanmar and Pakistan. The pathogens most strongly associated with disease were rotavirus, Shigella species and enterotoxigenic *Escherichia coli*[8]. These enteric pathogens, with cholera and typhoid fever, have been identified as the highest priorities for vaccination development by WHO[9].

Diarrhoeal episodes are usually acute and self-limiting. However, they can cause fluid and electrolyte loss from the small intestine so severe that it results in death from dehydration. In some cases, diarrhoea can become persistent: usually defined as lasting at least 14 d[10]. There is evidence that persistent diarrhoea in children can lead to malnutrition[11,12], growth stunting[13,14], and effects on cognitive function[15,16]. A Brazilian study found that children with persistent diarrhoea in the first 2 years of life scored significantly lower on intelligence tests at age 6-10 years, even when controlling for maternal education and helminthic infection[16].

In the late 1980s, oral rehydration therapy (ORT) transformed the management of acute diarrhoea. Physiological studies conducted during the 1950s and 1960s identified the co-transport of sodium and glucose in the small intestine[17-19], which were then harnessed into the oral rehydration solution (ORS) developed at the International Centre for Diarrhoeal Diseases Research in Bangladesh in 1968[20]. WHO adopted and started distribution of a standard ORS in 1975, and set up the WHO Programme for Diarrhoeal Control in 1979[21].

ORT has been heralded as one of the most important therapeutic advances of the past century and has undoubtedly contributed towards the reduction in global child mortality rates described above[22,23] (Figure 2). However it has not reduced the morbidity associated with diarrhoea. Neither stool volume nor

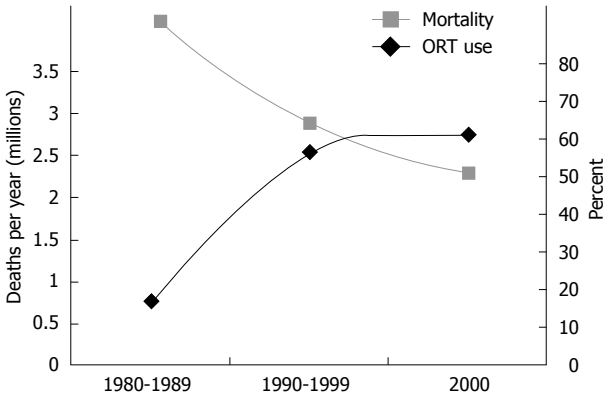

Figure 2 Association between coverage of oral rehydration therapy (ORT) use and mortality rates from diarrhoea in selected countries (from Podewils *et al*[23], 2004. Reproduced with kind permission of Elsevier).

duration of illness are significantly reduced with ORT use, and there may even be a paradoxical increase in stool volume. Therefore, further research has been performed on modifying ORT formulations, including the development of amino acid-containing, starch-based, and reduced sodium solutions. Glutamine, an amino acid, stimulates sodium absorption in experimental models of cholera and rotavirus diarrhoea[24-27]. However, there is conflicting evidence on the efficacy of glutamine containing ORT[20,28], and it is not recommended over WHO ORS at present. The rationale for starch-based solutions (either rice or cereals) is that the polysaccharides would provide more glucose at the intestinal mucosa without the large osmotic load of glucose-based formulations. In addition, they provide nutrition early in the illness. Cereal-based formulations have been shown to reduce total fluid requirements and duration of illness, and are recommended over standard ORS in patients with cholera (but not for non-cholera diarrhoea)[28]. Although cereal-based ORT should be more accessible in rural locations, one study showed that mothers found it more time-consuming to prepare and used standard ORT in preference[29]. In 2003, WHO modified its ORS formulation to contain a reduced amount of sodium and glucose. This hypotonic solution has been associated with less vomiting, decreased stool volume, and reduced need for intravenous fluids[30], and has been recommended for patients with non-cholera diarrhoea. However, concerns have been raised that exclusion of cholera can be difficult in under-resourced areas and use of this formula will lead to hyponatremia in these patients[31]. Clearly, there is still research to be done into the definitive formulation of ORT.

Despite the efficacy of ORT, uptake in developing countries can be variable[32,33]. Difficulties include remembering the correct quantities of ingredients involved in preparing an ORT and high levels of illiteracy[34-36]. Continued effort is required to provide ongoing education at a community level in order to bring about long-term changes[37-40].

More recently, it has been shown that zinc deficiency complicates a significant proportion of diarrhoeal cases[41]. Zinc is not stored in the body, and may be lost from the intestine during diarrhoea[42]. It has a role in immune function[43], however the physiological mechanism linking zinc deficiency with diarrhoea has not yet been elucidated. Several meta-analyses have shown that zinc replacement in acute and persistent diarrhoea reduces both the duration and severity of diarrhoea[43,44], and short (14 d) courses prevent further diarrhoea for 2-3 mo[45]. The WHO has recently recommended that zinc supplementation should be given to all children with acute diarrhoea persisting for at least 14 d[29]. Zinc supplementation has also been shown to significantly reduce the duration of lower respiratory infections[46], the second largest cause of child mortality worldwide.

Universal clean water, hygiene, and sanitation would be the ultimate solution to the global burden of diarrhoea, however in their continued absence, considerable interest has been shown in a more immediate intervention to prevent diarrhoea: vaccination. Of all the pathogens mentioned above, rotavirus is the leading cause of severe diarrhoea in children worldwide. By age 5 years, virtually all children will have been infected by rotavirus, and one in 293 children will have died from it. More than 80% of deaths from rotavirus infection occur in developing countries[47,48]. It also causes a significant financial burden in western countries. Each year in the United States, there are more than 400 000 consultations and up to 70 000 hospital admissions due to rotavirus[49]. Therefore, there has been substantial investment in the development of vaccines against rotavirus infections, both for western and developing countries.

In 2000 and 2001, China introduced a monovalent lamb-derived live attenuated oral vaccine[50]. However, the efficacy of this vaccine is not known, as it was not tested against placebo in the final stages. The focus of research in other countries has been on developing a vaccine against multiple rotavirus serotypes, in order to provide heterotypic protection[48]. The first multivalent live oral reassortant vaccine developed was RotaShield, which was highly effective in field trials in the United States, Finland and Venezuela[51-54]. It was included in the USA immunisation programme in 1998[55], however several cases of intussusception were reported, and the vaccine was subsequently withdrawn[56]. This risk was estimated to be only one per 10 000 vaccinated infants[57], however trials in Ghana, Bangladesh, and India were also stopped at that time, and it was thus not possible to do a risk-benefit analysis for developing countries[48]. Two further rotavirus vaccines have since come onto the market; Rotateq, a human-bovine live-attenuated oral vaccine, and Rotarix, a human live-attenuated oral vaccine. Trials in medium and high-income countries have produced good efficacy results for both these vaccines[58,59], however more trials are needed in developing countries. A large commitment to funding from donor countries will also be required to further reduce global child mortality from diarrhoea.

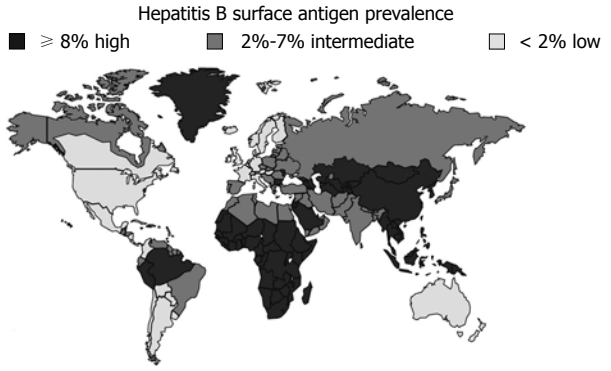

Figure 3 Geographical distribution of the prevalence of chronic hepatitis B virus infection, 2002 (from Mast *et al*[67], 2004. Reproduced with kind permission of Elsevier).

Hepatitis B virus (HBV)

Hepatitis B is the foremost hepatological health problem in the developing world. Up to two billion people worldwide have serological evidence of past or present HBV infection, and 360 million have chronic infection[60,61]. Through its long-term sequelae of liver cirrhosis and hepatocellular carcinoma (HCC), HBV causes 500 000-700 000 deaths each year[60] and is an accessible target for cancer prevention on a massive scale. Although hepatitis C virus (HCV) is increasing in importance, particularly in the western world, HBV is still estimated to account for 50%-55% of HCC worldwide compared to 25%-30% for HCV[62-64].

HBV varies in its prevalence worldwide. Countries can be divided by their level of endemicity, which is based on the percentage of the general population that is seropositive for HBsAg (chronic carriers). Countries with high endemicity have more than 7% seropositivity levels, intermediate 2%-7%, low 0.5%-2% and very low endemicity countries have < 0.5% seropositivity[65,66] (Figure 3[67]). Developing nations make up the bulk of high endemicity countries, including much of sub-Saharan Africa and South East Asia. Notable pre-vaccination examples include the Gambia, where 36% of children were chronic carriers[68], and Taiwan, with 15%-20% chronic carriage in the general population[69-71].

Of particular relevance to developing countries, the likelihood of acquiring chronic HBV infection depends on the age of acquisition of the virus[60,72,73]. For children under 1 year, the risk of chronic infection is 90%. For 1-5 years old, the risk is 30% and for children older than 5 years and adults, the risk decreases to only 6%. This feature accounts for most of the disparity in prevalence outlined above.

The main modes of transmission also vary between countries of high and low endemicity. In high endemicity countries, and in stark contrast to the West, perinatal and horizontal transmission (exposure from close household contacts or play with other children) are the dominant modes[66,74]. In these countries, 70%-90% of the population show serological evidence of previous or current HBV infection. In lower endemicity countries, HBV transmission is mainly limited to high risk groups, such as intravenous drug users and healthcare workers, or is acquired sexually. Although not the main transmission mode, healthcare-acquired infections can assume greater importance in developing countries due to lack of resources for disposable equipment and sterilisation, or lack of awareness of infection control practices[65,75]. However, blood products in most parts of the world are now screened for HBsAg[76].

Chronic infection is responsible for the main burden of disease associated with HBV. Approximately 20% of chronic carriers will die prematurely from cirrhosis leading to liver failure or HCC[77]. Although therapies are available which can suppress HBV replication or modulate the immune reaction, these are expensive and not widely available in much of the developing world. There is currently no therapy which results in virus eradication.

Therefore, the emergence of a plasma-derived vaccine against HBV in the early 1980s was a significant event. This was the world's first cancer prevention vaccine and the first vaccine to prevent a sexually transmitted disease, both functions now echoed by the recently licensed human papillomavirus vaccines. Most current vaccines are produced by recombinant technology[65], and the vaccine prevents HBV infection in 90%-100% of people who produce sufficient antibody responses[78]. It is also highly effective as post-exposure prophylaxis in cases of possible perinatal transmission, even where HBV immunoglobulin co-administration is not possible[79]. Current consensus is that booster doses are not necessary to maintain immunity[60]. Finally, although susceptible to freezing, present vaccines are heat stable, a great advantage in developing countries where access to cold storage facilities is often difficult[60].

In 1992, WHO's Global Advisory Group of the Expanded Programme on Immunization recommended that all highly endemic countries included hepatitis B vaccination into their national childhood immunisation programs by 1995, and all other countries by 1997[80,81]. As of 2006, more than 160 countries had implemented universal hepatitis B vaccination[82]. Several western countries with very low endemicity, such as the United Kingdom, have chosen to pursue a policy of targeted vaccination of high-risk groups rather than universal vaccination[83].

In countries which implemented universal childhood vaccination early on, such as Taiwan, the Gambia, and Malaysia, HBV vaccination was found to be very effective, both in terms of disease prevention and health costs[66,84]. The ultimate goal of these programmes is to prevent the long-term consequences of cirrhosis and HCC, therefore it will be some years before a complete evaluation can be carried out on the first vaccinated cohorts. However, indicators such as HBV seroprevalence and hospital records of acute HBV infections, provide early evidence of their successful impact.

In Malaysia, where universal vaccination was introduced in 1990, HBsAg seroprevalence among children aged 7-12 years decreased from 1.6% in 1997 to

0.3% in 2003[85]. In the Gambia, where HCC is the most common tumour in men[86], vaccination was introduced progressively between 1986 and 1990. Childhood HBsAg seroprevalence has since decreased from 10% in 1986 to 0.6% in 1991[87-89]. Similar declines have been shown in Senegal, China, Indonesia, and Thailand[90].

The best example of the effectiveness of a HBV vaccination programme is probably Taiwan, which had very high levels of chronic carriage in the pre-vaccination era[91]. Over 90% of the population under the age of 40 years had been infected by HBV[92]. Universal infant vaccination was introduced in Taiwan in 1984, one of the first regions to do so[91,93]. 15 years after implementation, HBsAg seroprevalence amongst children 1-15 years decreased from 9.8% in 1984 to 0.7%[94]. In addition, the incidence of fulminant hepatitis amongst infants also decreased. The average mortality from fulminant hepatitis in infants between 1975 and 1984 (pre-vaccination) and from 1985-1998 (post-vaccination) was 5.36 and 1.71 per 100 000 infants, respectively[95].

These evaluations show that HBV can be effectively prevented through a universal vaccination programme. As humans are the only known natural host of the virus, it is feasible that vaccination could eradicate HBV from the world. The major obstacle to global coverage of HBV vaccination is funding. Although the cost of monovalent HBV vaccines had decreased from approximately US $3.00 per dose in 1990 to US $0.30 per dose in 2001[96]. the cost is still higher than the other vaccines included in the extended programme on immunization (e.g. measles, oral polio) which cost between US $0.06 to 0.10 per dose. Several manufacturers have produced combination vaccines containing hepatitis B antigen which allow the addition of hepatitis B vaccine into existing childhood immunisation programmes, however again these are expensive and beyond the capacity of many developing countries.

The Global Alliance for Vaccines and Immunization (GAVI) was founded in 1999 to address this funding gap. GAVI is a consortium between WHO, the World Bank, UNICEF, the Bill and Melinda Gates Foundation, governments of both developing and developed nations, and the vaccine industry[97]. By 2007, it had provided funding for 67 countries out of 69 eligible for support towards the introduction of HBV vaccination programmes[98]. As a result, global three dose vaccine coverage has nearly doubled since 1999 (Figure 4[82]). However, the millions currently infected with HBV in the developing world carry an impending disease burden that will be substantial in the near future.

H pylori infection

It is estimated that 50% of the world's population is infected by *H pylori*[99]. Although most infections are not associated with clinical disease, a significant proportion will go on to develop some of the commonest problems in gastroenterology: gastritis, peptic ulcer disease, and gastric cancer[100-103]. Although less than one percent of infected persons will develop gastric cancer, this is the fourth most common malignancy in the world[104]. It is

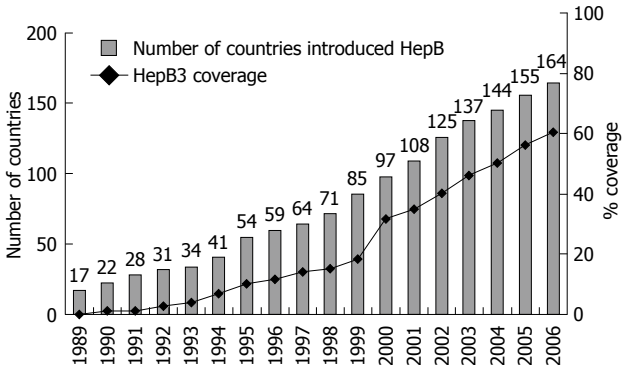

Figure 4 Graph showing number of countries who have introduced hepatitis B vaccination programme and global infant three dose vaccine coverage ("HepB3") (reproduced with kind permission of World Health Organisation).

Table 1 Estimated *H pylori* infection prevalence globally (reproduced with kind permission of World Gastroenterology Organisation)

Country/region	Estimated prevalence of *H pylori* infection (%)
Mexico, Central/South America	70-90
Africa	70-90
Asia	50-80
Eastern Europe	70
Western Europe	50-30
United States and Canada	30
Australia	20

these strong disease associations which establish *H pylori* infection as a leading gastroenterological public health problem.

There are distinct differences in the pattern of *H pylori* infection between developing and western countries. The prevalence of infection in the West has been declining for some years, however it is still very high in developing countries[99], with the majority of the global burden of infection found here (Table 1[105]). This is not surprising, given that risk factors for the infection include low socio-economic status, crowded living conditions, several children sleeping in one bed, large number of siblings and unclean water-all conditions common in the developing world[106-110]. Low education levels have also been positively associated with *H pylori* infection in several studies[111-113]. Prevalence levels in developing countries are therefore associated with the circumstances induced by poverty-and are unlikely to follow the decreasing trend of the western world without alleviation of this factor.

Another marked difference between *H pylori* infection in developing and western countries is the age at acquisition of the infection. Individuals tend to be infected much younger in developing countries than in western countries. In many developing countries, the prevalence of infection exceeds 50% by 5 years of age[114]. In a study of Bangladeshi children, the prevalence of *H pylori* infection was 42% by 2 years of age. Another study of Gambian children using the

diagnostic ^{13}C-urea breath test (UBT) found prevalence levels of over 75% in the second year of life[115] (although very young ages may produce false positive results in the UBT[116]). Comparative studies in western countries show prevalences ranging from 6% in Finland[117], 11% in Scotland[118], 13% in Germany[119], and 23% in Italy[120,121].

Epidemiological studies support person-to-person transmission, which is likely to be *via* faecal-oral and oral-oral routes[122]. The oral-oral route is supported by the finding that pre-mastication of food (the chewing of food by mothers before feeding their babies) is associated with increased prevalence of *H pylori* in infants[106,123,124]. Pre-mastication of food is a common practice in both South-East Asia and Africa. Water sources have also been implicated as a potential mode of transmission, possibly through faecal contamination. An early Peruvian study showed that children living in households with a municipal water supply had a markedly higher risk of *H pylori* infection compared to those who had access to well water[125]. This was supported by findings from a study in Bolivia which found that children living in families using containers which prevented direct contact with this drinking water were significantly less likely to have *H pylori* infection compared to families without this container[126]. Iatrogenic transmission through contaminated endoscopes has been documented both in western and developing countries[127-129], and may be a particular problem in those countries where lack of resources hinders full disinfection procedures[130].

Worldwide, 90% of duodenal ulcers and up to 70% of gastric ulcers are associated with *H pylori* infection[100]. However, peptic ulcer disease is more likely to be reported in western countries, whereas gastric carcinoma is the more common disease association in developing countries[131] In 1994, the International Agency for Research into Cancer designated *H pylori* as a Class I Carcinogen[132].

It is hypothesized that the global variance in disease presentation is related to the age of acquisition of *H pylori* infection[101,122,133]. Infections acquired early in childhood, as in most developing countries, may cause persistent chronic low-grade inflammation which is linked with gastric cancer. Conversely, infections acquired later in life or in adulthood are associated with a more acute inflammatory response and thus ulcer disease.

However, differing incidence rates of gastric cancer globally has led to the description of the "African enigma": that despite a high prevalence of *H pylori* infection, this region has a relatively low incidence of gastric cancer[114,134]. However, this description has been disputed as the average life expectancy on the continent is low (51 years in 2006)[6]. Therefore, individuals may die of other causes before an age at which gastric cancer would become apparent. Indeed, a recent review by Agha *et al*[135] of endoscopy studies carried out on the continent found that *H pylori*-associated peptic ulcers and gastric cancer occurred at similar rates to Western levels.

H pylori infection can have significant sequelae in children in developing countries in addition to the long-term effects of chronic inflammation. Acute *H pylori* infection induces hypochlorhydria, which can be persistent[136-138]. Hypochlorhydria is associated with an increased risk of diarrhoeal diseases, as the gastric acid barrier is effective against many enteric pathogens[139,140]. Therefore, children infected with *H pylori* may be more likely to suffer from diarrhoeal diseases, both acute and persistent[140-143]. In fact, similar findings of malnutrition and decreased growth to those described above for diarrhoeal diseases have been shown in children infected with *H pylori*[142,144-146].

Spontaneous remission of *H pylori* is rare. For symptomatic infections, eradication is usually achieved by a course of antibiotics (typically clarithromycin, amoxicillin or metronidazole) combined with a proton-pump inhibitor[147]. There are other regional guidelines which recommend specific combinations, some of which are directed towards cost issues[148,149]. However, low-cost options may not be as effective as more expensive regimes and may necessitate repeat treatment, leading to higher costs overall[105]. In addition, although eradication may be achievable in western countries with a 7 d regime, treatments of 14 d may be required in developing countries. A study from Brazil showed eradication rates of only 50% if therapy was less than 10 d[150]. Subsequently, a meta-analysis showed a 12% higher eradication rate for 14 d *versus* 7 d regimes[151]. This must be balanced against the likelihood of patient compliance to a complex regime of drugs for 2 wk.

Unfortunately, eradication has been increasingly affected by antibiotic resistance levels worldwide. Many antibiotics are available "over the counter" in developing countries, i.e. not subject to prescription from a doctor. Metronidazole is also used to treat common enteric infections such as amoebiasis and giardiasis: often empirically. Metronidazole resistance is an increasing problem worldwide, although may not affect eradication as much as clarithromycin resistance[114,147]. Antibiotic resistance is the main reason for treatment failure. If sensitivity testing is available, this should guide choices for local first-choice and rescue therapy[105,147].

Re-infection rates after eradication can be as low as 1% in western countries[114]. Given the much greater prevalence of *H pylori* infection in developing countries, it is not surprising that re-infection rates there are also markedly higher. Studies from Chile and Bangladesh have found re-infection rates of around 13%[152,153]. It was difficult, however, to distinguish re-infection from recrudescence in these studies[114].

These issues highlight the need for a vaccine against *H pylori*. As for HBV, there is a need for both preventative and therapeutic vaccines, with the preventative vaccine used primarily on young children in high prevalence areas. Rupnow *et al*[154] modelled the population impact of a prophylactic vaccine. For a typical developing country, they found that with continuous vaccination, *H pylori*-attributable gastric cancer would decrease from 31.8 per 100 000 to 5.8 per 100 000 by 2100. Unfortunately, the current status of *H pylori* vaccines is disappointing. A number of trials have been conducted examining the safety and immunogenicity of various

formulations including recombinant urease, killed whole cells, and live vectors expressing *H pylori* antigens[155]. However, the vast majority of these showed low immunogenicity. Further research is needed to elucidate the mechanism of immune protection and the role of adjuvants.

In conclusion, *H pylori* infection is recognised as a significant public health problem in developing countries. Both antibiotic resistance and re-infection rates threaten the efficacy of existing eradication therapy. Definitive treatment in the form of both prophylactic and therapeutic vaccines is urgently needed in order to alleviate the burden of disease associated with this bacterium.

DELIVERY OF CLINICAL SERVICES IN DEVELOPING COUNTRIES

The first part of this review described three major gastroenterological diseases in the developing world: diarrhoeal disease, hepatitis B, and *H pylori*. Given this burden of gastroenterological disease, specialists in gastroenterology and hepatology are particularly important in developing countries. However, as in most specialities, there is a shortage of trainees.

Mass education and vaccination programmes against diarrhoeal infections, HBV, and potentially *H pylori*, all require immense resources for delivery. Dissemination of the ORT message requires health workers trained in education and prepared to work in remote areas. The consequences of HBV and *H pylori* infection are optimally treated by specialist referral and endoscopy services. However, one of the most limiting factors in the delivery of clinical services in developing countries is the severe lack of trained healthcare personnel.

Health workers

WHO estimates that there is a global shortage of 4.3 million healthcare workers. Africa alone needs an estimated 1.5 million more health workers in order to provide just basic health services[156]. For many years, the strengthening of national health systems and training of personnel have not been included as part of international aid programmes[157]. Staff have been mainly trained intensively for a particular programme's focus, with little integration into a comprehensive national system of health workers.

The result is an uneven distribution of health workers, inverse to the world's health needs. The Americas, including Canada and the United States, have 10% of the global burden of disease, yet almost 37% of the world's health workers. Sub-Saharan Africa, conversely, has more than 24% of the disease burden, yet has only 3% of health workers and less than 1% of the world's financial resources[156]. Ethiopia, for example, has two doctors per 100 000 population. The UK has more than 230 per 100 000[2] (Figure 5[156]). Fifty-seven countries are estimated to have critical shortages of health workers: 36 in sub-Saharan Africa[156].

Figure 5 Geographical distribution of countries with a critical shortage of health service providers (doctors, nurses and midwives) (reproduced with kind permission of World Health Organisation).

There is also a great imbalance within countries. Many hospitals and medical centres are centred in urban areas, whilst populations of many developing countries are still predominantly rural. In both developing and western countries, highly skilled workers can resist rural postings, as there is a higher quality of life and opportunity for money in the urban areas[157,158]. In Malawi, 85% of the population live in rural areas[2]. However, out of Malawi's 156 public sector doctors, 81 are working in central hospitals[159,160]. This leaves many districts without any doctors at all.

There is a general perception that economic migration by skilled health professionals is the main cause of the global shortage. There has been debate in western countries over the ethics of wealthy, more developed countries with a relative density of health workers accepting highly skilled medical migrants from countries with a severe need and valuable investment in their initial training[161]. It is estimated that the UK has saved some £65 million in training costs between 1998 and 2002 by recruiting Ghanaian doctors[162], whilst Ghana has lost £35 million of its training investment to the UK. However, although migration certainly plays a part, it is not the major factor. If Ethiopia had all the doctors it had trained over the last 30 years, there would still only be approximately ten doctors per 100 000 population[157]. The total number of African-born doctors and nurses working in Organisation for Economic Co-operative and Development countries account for less than 12% of the estimated shortages in Africa[163]. (While migration may not account for overall shortages in medical manpower its effects appear to be especially felt among highly trained specialists. In some developing countries almost 100% of specialists leave the country; most never to return).

There are not enough healthcare professionals being trained in developing countries to sustain the needs of the population. Ethiopia produces about 200 doctors per year for 75 million population[164]. The UK produces 6000 per year for 60 million people. Two thirds of Sub-Saharan African countries have only one medical school, whilst some still have none[165]. This inadequate production of health professionals, combined with the accumulative effects of migration and losses due

to the HIV/AIDS epidemic (44 Malawian nurses died in 1999-44% of the annual number trained)[166] have resulted in the severe shortages seen today.

There are several reasons for this low production rate of health workers. Foremost of these, inevitably, is funding. WHO estimates that it would cost $26.4 billion dollars to train the extra 1.5 million health workers needed for the African region, not including provision for future salary costs[156]. Any extra training or production of healthcare workers would require great motivation by donor agencies and governments to provide sustainable funding. Firstly, there is a high rate of student and teacher attrition. Students often find it difficult to find sufficient funding for tuition fees, even with government subsidies. Students who have received poorer quality secondary education may struggle with a medical course, and there is often little support available. Health worker shortages inevitably affect teacher numbers, with remaining lecturers shouldering an increased workload[157].

Once qualified, new graduates are faced with difficult working conditions. Lack of resources can lead to poor job satisfaction and high levels of HIV seropositivity make practical procedures hazardous[156,158]. There has also been a tendency to focus on pre-service training to produce health workers, compared to postgraduate education. Opportunities for specialisation and career progression are few[167]. For example, in Malawi, only 5% of medical specialists and 8% of paediatric posts are filled[159,160]. Salaries which are not adequate to cover living costs make posts in western countries very appealing. In 2004, a junior doctor in Malawi earned approximately £1900 per annum[160]. Basic annual pay for a pre-registration house officer in the UK is £21 000[168]. Indeed, there may be strong family pressures to take a job overseas and provide valuable remittances for those who remain in the country. Some countries have actively embraced health worker migration as a source of revenue. The Philippines operates a managed migration policy and is now the largest provider of registered nurses working overseas[158]. However, 30 000 nurse posts are currently unfilled in the Philippines[158].

The consequences of all these factors on a medical specialty are amply illustrated by the situation in gastroenterology. The world-wide burden of digestive illness is tremendous; for example, digestive cancers, collectively, are the most common malignant diseases. Furthermore, while infectious diseases, as illustrated in the first section, represent a major and persisting challenge for developing nations, urbanization and westernization now threaten to inflict the gastroenterological problems of the West, such as those related to obesity[169] on these already underserved populations. In addition, in certain developing countries prevalence rates for gastroenterological disorders which are very rare in the West, such as gall bladder and biliary cancer, are high and a public health issue. Yet many African countries possess not a single gastroenterologist. Though some would argue that more basic medical care should be the priority in these countries, the World Gastroenterology Organisation (WGO) would counter that to deprive these countries of the expertise that specialists and sub-specialists can provide is condescending, to say the least. If nothing else, such expertise is needed to assist in health care provision planning. It should come as no surprise, therefore, that the many advances in the field of gastroenterology which have so dramatically advanced patient care and improved mortality and morbidity in the West, have not been evenly bestowed on the world's population; some areas of our planet have barely felt the impact of advances in diagnostics and therapeutics. A very striking example is provided by the failure of the laparoscopic era which has so revolutionized digestive surgery elsewhere to even dawn in many African countries. Lack of resources is certainly a factor but lack of skilled personnel is also contributory. Similarly, in many African countries none save for the most privileged have access to diagnostic services, such as endoscopy and ultrasound, that would be deemed routine elsewhere.

More global attention has been paid to the issue of health worker shortages over the last few years. The World Health Report in 2006[156] was dedicated to the health worker crisis. The Global Workforce Alliance, which is hosted by WHO, was set up later in 2006 in order to collate and implement effective strategies to tackle the shortages. In 2008, the first Global Forum on Human Resources for Health was held in Uganda.

Given the urgency of the problem, there is a consensus that innovative solutions are needed rather than simply increasing the number of medical training places. One approach, which has been successful in several developing countries, has been to shift away from a western-style distribution of health workers. Low- and medium-level workers, such as community workers and nursing auxiliaries, can be more appropriate for the needs of the population rather than dependence on high-level workers such as doctors and nurses[157]. Not only is there a greatly reduced training time for these lower-level workers, but more workers can be produced for the same training investment and salary costs are lower. In addition, these workers do not have internationally recognised qualifications, and therefore are less likely to emigrate[157,158]. Although high-level workers are still needed for supervision, some countries have had great success in achieving basic health coverage with community workers.

In 1994, Pakistan created the Lady Health Worker (LHW) cadre, aiming to train 100 000 female community health workers by 2005[157]. These workers are recommended by their community, usually in rural and urban slum areas, and are trained for 15 mo in the prevention and treatment of common illnesses. An evaluation of the scheme in 2002 found that populations served by a LHW are more likely to adopt antenatal care, receive medical assistance at birth, and use family planning services[170]. In Malawi, there is a high rate of trauma associated with farming and road traffic accidents, but only nine orthopaedic surgeons[171]. Orthopaedic clinical officers (OCO) are specifically

trained over 18 mo to be able to fulfil most of the orthopaedic roles required in rural district hospitals, including the conservative management of fractures and dislocations, and some external fixation methods. Since the programme began in 1985, it has trained 117 OCOs, who now manage an estimated 80% to 90% of the orthopaedic workload in Malawi[171]. Indeed, a reliance on western-style models of health workforces has meant that in sub-Saharan Africa low and mid-level workers make up only 7% of the workforce, compared to around 20% in Brazil and Iran[172].

It has also been commented that western models of medical curricula may not be appropriate for countries with an urgent need for health workers. A 5-year course with a strong focus on basic sciences may be a luxury in developing countries with high levels of communicable diseases and limited resources. The St Paul's Millennium Medical School in Ethiopia was set up by the government as part of its aim to increase the national production of doctors to 1000 per year[157]. Here, the curriculum has been cut down from 5.5 to 3.5 years, with an emphasis on practical skills, in order to better prepare graduates for their 5 years service in rural hospitals (Professor Gordon Williams, Dean of St Paul's, personal communication).

Internationally, there have been several bilateral agreements which aim to promote ethical recruitment in response to criticism of western countries' active recruitment of foreign health workers. The UK-South Africa Memorandum of Understanding was signed in 2003 and aims to decrease the efflux of South African health workers through efforts to offer time-limited placements as alternatives and to promote UK self-sufficiency[173]. Norway is also developing a policy which will invest in health worker development projects, whilst increasing the number of national training places to encourage self-sufficiency[173]. Changes under the new UK career progression scheme Modernising Medical Careers is also likely to have an effect on international recruitment. For all training posts, UK graduates and those from the European Economic Area are prioritised over international medical graduates[174]. Although prompted by efforts to improve NHS stability and secure training places for all UK graduates rather than ethical concerns, this policy is likely to decrease the attractiveness of the UK medical job market abroad.

If health workers increasingly remain in their home country, further training must be made available in order to provide adequate numbers of specialists and promote more advanced skills. For gastroenterology specialist training, the main advocate is the WGO. The current objectives of WGO are enshrined in its mission statement: "to promote, to the general public and health care professionals alike, an awareness of the world wide prevalence and optimal care of digestive disorders through the provision of high quality, accessible and independent education and training", which signals the commitment of WGO to address two challenges: firstly, providing the gastroenterologist of the future with an optimal training and, secondly, and most pertinent to this review, bringing the benefits of digestive health care to those who currently struggle or, indeed, fail to achieve access to it. The primary emphasis of WGO, therefore, is on education and training; these objectives are achieved through three distinctive, though closely inter-related, programmes: Training Centres, Train-the-Trainers, and Global Guidelines (described later in review).

Figure 6 Map showing location of World Gastroenterology Training Centres worldwide (reproduced with kind permission of World Gastroenterology Organisation).

Training Centres most directly address the issue of training specialists in gastroenterology or individuals with additional expertise in gastroenterology to serve previously underserved areas. Each centre represents a direct collaboration between local experts, international faculty and several national and regional societies from Europe and North America to deliver regionally relevant training to those who have limited, or in some cases, no access to such opportunities. Our centres in South Africa, Morocco, Egypt, Bolivia, Pakistan, Thailand, Mexico City and Fiji (Figure 6) provide training of variable duration to several hundred young and aspiring gastroenterologists and digestive surgeons from underserved nations in their region. In some of these instances, such as in the centres in Soweto and Suva, the focus is on providing training opportunities to young doctors from areas where little or no gastroenterological expertise exists (in these cases Sub-Saharan Africa and Oceania, respectively). More recently, WGO has established partnerships with centres in Italy, Chile, Argentina, and Brazil to provide more advanced training opportunities to the young doctor who has already completed basic training.

Activities at these training centres are supported by other linked WGO programmes. Train-the-Trainers courses are uniquely devoted to bringing the very latest in educational techniques to those who will train the gastroenterologists of the future, including those who teach and train at our Training Centres. These networks should be accessible to all who seek to train in our specialty, thereby, ensuring the highest standards of care for those who suffer from digestive disorders through the world.

Clinical services

The limiting effect of the shortage of trained health workers and specialists can be seen in the central clinical service of gastroenterology: endoscopy.

In western countries, endoscopy services have

Figure 7 Cut Foley urethral catheter reloaded unto the Opti-vu cap for variceal band ligation at the Endoscopy Unit of Jos University Teaching Hospital, Nigeria.

become such a routine procedure that facilities are readily available, even in some primary care centers. However, in developing countries, services are only available in so-called "centers of excellence" and are rudimentary in most circumstances. They often comprise of direct viewing fibre-optic endoscopes only and are mostly restricted to diagnostic gastroscopies.

This difference is not surprising due to the numerous challenges posed by establishing endoscopy units, including training needs, adequate disinfection facilities and equipment. There is also a lack of awareness amongst most healthcare professionals of the usefulness of therapeutic endoscopy.

While the overall picture looks bleak, there have been some attempts by developing country gastroenterologists to establish endoscopy services. Variceal haemorrhage from portal hypertension is associated with high mortality in most West African countries, due to the lack of endoscopic banding facilities[175]. The Endoscopy Unit at Jos University Teaching Hospital in Nigeria has recently started to perform oesophageal variceal banding and injection sclerotherapy. It costs approximately $300 USD for a single use variceal band ligator, which is vastly prohibitive for most developing country workers. Therefore, the gastroenterologists working at the Endoscopy Unit have modified the normal variceal banding technique by cutting size 14 Foley urethral catheters to size and reloading these on previously used Opti-vu caps (Figure 7). Although not optimal practice, this has reduced the cost to only $30 per session. The modified technique has allowed much greater uptake of the procedure, with improved clinical outcomes. If such interventions become widespread nationally, it has the potential to markedly improve the prognosis in complications of end-stage liver disease, which currently carries a significantly burden in Nigeria.

The training programme for Nigerian gastroenterologists in endoscopic therapies has been bolstered by Royal College of Physicians educational bursaries, which have allowed visits to the UK and reciprocal visits to Nigeria. The Tropical Health and Education Trust also provides training for frontline health workers in the poorest settings, and develops the institutional capacity of local health institutions. This is achieved by focusing on the goals of local health care specialists in individual hospitals, clinics and primary health care projects and offering specialist support and training from UK-based health professionals on a one-to-one basis. Finally, the World Organization of Digestive Endoscopy has set up training centres in Cairo, Egypt and Soweto, South Africa with the aim of improving the management of gastrointestinal disorders in sub Saharan Africa.

It is evident that effective clinical services can exist in developing countries despite being tailored to available resources. Difficulty in adhering to western-defined standards should not necessarily inhibit medical action with benefit to the population.

Guidelines and cascades

Numerous guidelines are produced annually by prestigious medical bodies. The vast majority of these outline "gold standard" practice and are aimed at physicians in resource-rich environments. As such, they are inaccessible and irrelevant for many clinicians in developing countries. As in the case of endoscopy above, many clinicians in developing countries have to "make do" with available resources: in full knowledge that this falls below the gold standard. However, by failing to acknowledge this situation and providing the "next-best option", western guidelines may be preventing the dissemination of knowledge and evidence to its full global audience[176-179].

In order to make guidelines more applicable to differing resource environments, the concept of "cascades" have been developed[177,180]. A cascade is a collection of related diagnostic and treatment options arranged hierarchically in terms of conditions and available resources. Whilst guidelines should continue to summarise best known practice, they could also include alternatives for clinicians with limited funding. These alternatives are usually on the basis of cost, but could also take account of local availability, technology, and infrastructure. Cascades can range from a simple list of options (Table 2) to more complex parallel diagnostic and treatment pathways (Figure 8). In this way, they transform guidelines from being "resource-blind" to "resource-sensitive". Inevitably, cascades are more heavily based on empirical evidence than gold standard options. Research funding is usually spent on trying to improve on best practice-rather than the practicalities of delivery in developing countries. However, with strong involvement from experienced clinicians in developing countries, a consensus is usually reached. More widespread use of cascades in guidelines may also motivate research into the best options for resource-limited services.

Several organizations are now using cascades regularly in their work. The WGO is aiming to include cascades in all of its new guidelines, and has so far published on *H pylori*, acute diarrhoea, treatment of oesophageal varices, colorectal cancer, and hepatitis B[105,181-184]. To aid dissemination, most WGO guidelines are available in at

Table 2 Cascade for treatment of oesophageal varices (reproduced with kind permission of WGO)

Endoscopic band ligation plus octreotide or terlipressin (gold standard)
Endoscopic band ligation alone
Endoscopic sclerotherapy
Balloon tamponade

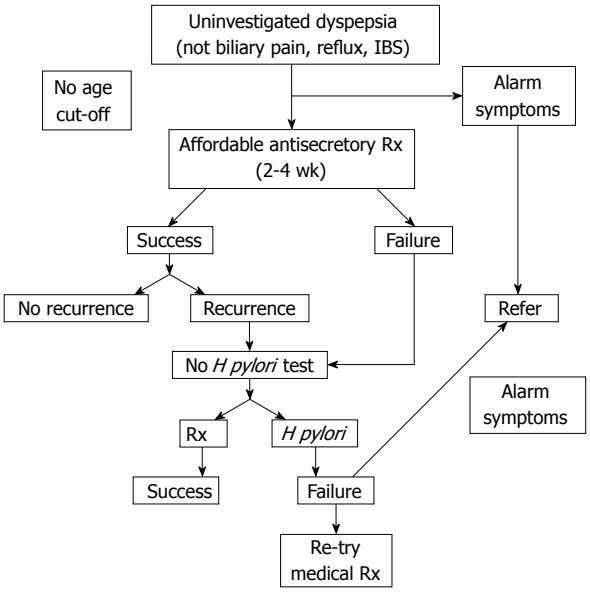

Figure 8 A more complicated cascade for management of dyspepsia in a region with a high prevalence of *H pylori* infection but limited access to endoscopy (reproduced with kind permission of WGO). IBS: Irritable bowel syndrome; Rx: Retreatment; Success: Symptoms resolve; Failure: Symptoms persist.

least four languages; downloads of non-English versions now account for more than 50% of website traffic. The Asian Pacific Consensus on the msanagement of *H pylori* was an early piece of work produced in response to the need for regional guidelines which took account of resource limitations[149]. A programme which uses cascades in response to the urgent need for improved early detection and basic treatment of breast cancer in developing countries is the Breast Health Global Initiative[185,186]. This is an international alliance of health organizations, government agencies, and leading clinicians, which recognises the inflexibility of western-developed screening programmes and aims to produce evidence-based and economically feasible guidelines for medium and low resource regions.

CONCLUSION

The first part of this review has described the disparity between developing and developed countries for three prominent public health problems: diarrhoeal diseases, hepatitis B, and *H pylori*. In this second section, we have considered some of the major obstacles developing countries face in the delivery of gastroenterological services. Increased investment into health workers worldwide is long overdue. Using endoscopy as an example, some of the current difficulties in clinical services implementation in developing countries were highlighted. Finally, guidelines which acknowledge and adapt to the reality of resource limitations would greatly improve information delivery worldwide.

Ultimately, however, perhaps the most important factor needed to improve healthcare in developing countries is the alleviation of poverty. A report in 2001 from the Commission on Macroeconomics and Health[187] showed a negative correlation between the infant mortality rate of a country and the rate of growth of their gross domestic product-the lower the mortality rate, the faster the growth of the economy. An improved economy would allow more investment in sanitation, housing, water quality: all factors which would effectively reduce the prevalence of the diseases discussed above. Until then, however, we must increase recognition of the varying situations facing gastroenterological colleagues worldwide.

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