Preventing malaria in endemic areas

Policymakers should remember that indoor residual spraying is highly effective

JULIO ETCHART/STILL PICTURES

RESEARCH, p 1023

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About 40% of the world's population, most of whom live in the poorest countries, are at risk from malaria. In Africa alone, malaria kills nearly a million children each year.[1] Although we have the tools to fight malaria, such as insecticides for indoor residual spraying, environmentalist campaigns and some ill conceived decisions on public health policy have limited their use.

A renewed effort is under way to control malaria in sub-Saharan Africa. While heartening, the lead agencies have neglected to rebuild the technical expertise necessary to run effective vertical malaria control programmes. Still cautious of DDT (dichlorodiphenyltrichloroethane) and indoor residual spraying, such programmes have focused on the distribution of bed nets impregnated with insecticides. In this week's *BMJ*, Hill and colleagues assess the effect of combining an insect repellent with insecticide treated bed nets on *Plasmodium falciparum* or *P vivax* malaria in Bolivia.[2] The trial found that people who used treated nets and repellent had an 80% reduction in *P vivax* episodes compared with those who used treated nets alone (incidence rate ratio 0.2, 95% confidence interval 0.11 to 0.38). The number of cases of *P falciparum* during the study was small and, after adjustment for age, a protective effect of 82% was seen, although this was not significant (0.18, 0.02 to 1.4).

The authors describe the many barriers that mosquitoes must overcome to bite and transmit malaria indoors. The first barrier, the house wall, deters most mosquitoes—the more tightly enclosed the house, the more effective this barrier is. If the house wall is sprayed with a spatial repellent like DDT, then it becomes an even better barrier. However, Hill and colleagues' study focused on two other barriers. The first was lemon eucalyptus—a topical insect repellent—which was applied to the skin in the early evening to deter insects from biting. Lemon eucalyptus is a contact irritant, which agitates mosquitoes when they come into physical contact with the chemical residue (J Grieco and N Achee, personal communication, 2007). The second barrier comprised bed nets treated with a pyrethroid insecticide. The first and dominant action of this insecticide is contact irritancy. Mosquitoes become agitated when they land on the netting.[3 4] They might then leave the house without biting or bite an unprotected person in the house before leaving. In addition, the insecticide kills mosquitoes that have more prolonged contact with netting.

However, despite the strengths in the theory and design of the study, the results show that using impregnated bed nets alone did not adequately reduce rates of malaria. The annual parasite index (number of cases of malaria per 1000 people each year) is a standard measure of the extent of malarial infection in human populations. If the numbers of cases of *P vivax* for the intervention and control groups are converted to annual parasite indexes, they are unacceptably high—more than 21 for the combined intervention group and more than 32 for the group using bed nets alone. Even these high values are underestimates because no data were presented for infections in children under 10 years. In addition, only the first infection with vivax malaria was included in the analysis, and subsequent infections were not analysed.

To illustrate how high the annual parasite indexes are in the study, when DDT was used for indoor residual spraying, malaria endemic areas of Bolivia typically had values below one. Index values increased only during years of declining use of DDT.[5] This remarkable effectiveness was attributable mostly to the spatial repellent action of DDT on house walls.[6 7] So, although Hill and colleagues' trial looks at the long neglected use of repellents for controlling malaria, indoor residual spraying with DDT is a much more effective way to control this disease. Unfortunately, spray programmes have gradually been eliminated. As a result, high rates of malaria have returned to Bolivia, as the Hill study shows.

The free distribution of insecticide treated bed nets halved child deaths in Kenya.[8] This encouraging result led the World Health Organization to endorse the free distribution of treated bed nets. People and organisations who promote treated bed nets often suggest that indoor residual spraying is not sustainable because of the need for infrastructure, but even a programme that promotes the distribution of free bed nets needs infrastructure. Bed nets have to be procured and distributed, people need to be told how to use them properly, user compliance needs to be monitored, and disease surveillance is required. In addition, the number of child deaths, not the amount of disease within populations, is used to assess the success of treated bed nets. As suggested by Hill and colleagues study, evaluations of bed nets that rely on amount of disease show far less efficacy than evaluations that use child deaths as an end point. Hill and colleagues did not record child deaths, and their results show that

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treated bed nets do not adequately control malaria. This contrasts sharply with the high and continuous levels of control achieved in Bolivia when house walls were sprayed with DDT.

All available tools are needed to control malaria. However, those who promote treated bed nets should stop using the need for infrastructure as an argument against the use of indoor residual spraying, because infrastructure is needed for bed nets too. Furthermore, child deaths and disease rates should both be used when assessing the effectiveness of control programmes.

The Bill and Melinda Gates Foundation stands alone today in investing in research, through the innovative vector control consortium, for new chemical tools to control malaria. But much more is needed and public funds should be made available for research to develop new spatial and topical repellents, contact irritants, and innovative modes of toxic action.

The trial by Hill and colleagues raises intriguing questions, such as can high levels of control be achieved through the spatial repellent activity or contact irritant activity of non-toxic chemicals? And, will non-toxic chemicals that modify behaviour select for resistance? Instead of supporting impregnated bed nets alone, public health agencies should invest more in finding the answers to these questions and increasing our arsenal of chemicals to control malaria.

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Improving adherence to drugs for hypertension

General practitioners who provide effective explanations of treatment achieve better results

RESEARCH, p 1030

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Effective drug treatments are available for many chronic conditions. But management of chronic diseases can be successful only if health professionals prescribe appropriately and if drugs are taken appropriately to maximise their pharmacological effects. A systematic review of interventions to improve adherence stated that, "ways to help people follow medical treatments could have far larger effects on health than any treatment itself."[1] Interventions to improve adherence in people with hypertension have targeted patients and health professionals, but studies in the past have often lacked methodological rigour.

Adherence to long term treatment for chronic illnesses in developed countries is about 50%, and rates are probably even lower in developing countries.[2] In this week's *BMJ*, Qureshi and colleagues report the results of a cluster randomised controlled trial of a simple educational package delivered to 78 general practitioners in Karachi, Pakistan.[3] The intervention consisted of a one day "intensive training session" that covered knowledge and skills needed for the management of hypertension and included "explanations of therapy and use of appropriate communication strategies." The trial included 200 people aged 40 or over with high blood pressure who were taking antihypertensive drugs. Adherence, defined as "correct dosing" (the proportion of doses taken), was measured using electronic drug monitors, and 178 of the participants completed the six week follow-up. The study took place six months after the general practitioners' training session. Adherence was significantly higher in the intervention group. Subgroup analysis of people with good versus poor adherence showed a clinically important decline in systolic (8.3 mm Hg; P=0.04) and diastolic blood pressure (3.8 mm Hg; P=0.1). In a country with relatively low levels of blood pressure control and a high prevalence of hypertension, the results of this study are encouraging.[4]

The study is important because it is a randomised controlled trial that uses a pragmatic intervention. Electronic drug monitoring, one of the more reliable methods of measuring adherence, was used to measure outcomes. The study has limitations—although the intervention seemed to be effective, it tells us little about which parts of the intervention helped increase adherence. We also do not know whether the effect is likely to be sustained because the follow-up period of six weeks is short, especially as treatment for this condition is usually life long.

Randomised controlled trials of interventions to improve adherence have found that no simple interventions and only a few complex ones (interventions built up from several components, which may act independently and interdependently)[5] are effective. In general, they have led to small improvements in adherence.[1 6 7] In hypertension specifically, reducing the number of doses and simplifying drug regimens as well as some complex interventions seem to be effective.[8] Educational interventions aimed at health professionals and patients are unlikely to result in clinically

important reductions in blood pressure. An organised system of regular follow-up is probably the best way to achieve adequate blood pressure control.[9]

The association between adherence and control of blood pressure is far from clear. Adherence to drugs that lower blood pressure seems to be higher in randomised trials than in observational studies, perhaps because of a selection bias towards more motivated participants.[10] In addition, adherence to treatment may vary between people with newly diagnosed hypertension and those with established disease.

Suboptimal adherence to prescribed drugs is a global health problem, and international and national initiatives have looked at ways to improve adherence, particularly in chronic conditions.[2 11] Many studies in the past were of poor methodological quality. Any interventions that aim to increase drug adherence in primary care will probably be complex and will need to be developed rigorously.[5] Funding bodies should take the need for development of interventions seriously and provide resources for conducting pilot work.

When dealing with a patient with hypertension who has not reached his or her target blood pressure, adherence to drugs is just one of several areas of management that need to be considered, including errors of measurement, white coat syndrome, antagonising drugs, and secondary hypertension.[12] In this context, Qureshi and colleagues show that providing explanations and communicating with patients can enhance adherence and may also improve blood pressure control.

In addition to primary preventive measures, people with high blood pressure in both developed and developing countries need access to effective antihypertensive drugs. Particularly in settings where drug adherence is low, people will be more likely to take their drugs if health professionals have knowledge and skills in improving adherence. As Qureshi and colleagues' study shows, education of health professionals can achieve this goal.[3]

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Maternal and neonatal effects of caesarean section

More accurate estimates of benefits and harms are needed to support informed childbirth choices

RESEARCH, p 1025

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Rising rates of caesarean section have stimulated much research and debate in the international medical literature. The proportion of caesarean sections in Australia climbed from 19.4% of all births in 1994[1] to 29.1% by 2004.[2] Already high figures in the United States had risen further to 30.2% by 2005,[3] similar to the 33% seen for Latin America in the same year.[4] Despite its growing acceptance as an alternative to vaginal birth, caesarean section is not benign surgery. In their paper in this week's journal, Villar and colleagues add to the growing body of evidence that cautions against high rates of caesarean delivery. The study supports the notion that caesarean section is justified only when benefits outweigh harms.[4]

The prospective cohort study uses a rich dataset from Latin America, the earlier results of which have been published previously.[5] The study clearly shows that high rates of caesarean section do not necessarily produce better health outcomes for mothers and babies. For the 97 095 births studied, severe maternal morbidity was significantly more likely with caesarean section (odds ratio 2.0, 95% confidence interval 1.6 to 2.5). Neonatal outcomes were closely related to fetal presentation at birth.[4] Fetal mortality of 9.69% and neonatal mortality (until discharge) of 8.55% were reported for vaginal breech birth, compared with 0.96% and 1.79% for elective caesarean section.[4] The authors conclude that elective caesarean section had a protective effect for breech presentation in this group of women. However, protective effects against fetal death for cephalic presentation were less obvious, with significantly higher neonatal mortality (until discharge) associated with both elective and intrapartum caesarean section.[4]

Large population based studies, case control studies, and retrospective cohort analyses have warned against potential adverse surgical outcomes from caesarean section for mothers and babies. They report higher rates of stay in neonatal intensive care for longer than seven days, higher rates of maternal hospital stay longer than seven days,[5] greater need for maternal readmission to hospital in the postpartum period,[6] and higher rates

of maternal mortality as a result of complications of anaesthesia, infection, and venous thromboembolism.[7] Longer term effects include increased risk of placenta praevia, placenta accreta, and abruption in subsequent pregnancies[8 9] and possible association with stillbirth in future pregnancies.[10 11] Concerns have also been raised about links between caesarean section and neonatal morbidity[5] and mortality,[12] even when possible confounding variables are taken into account.

Caesarean surgery can cause iatrogenic problems in the same way that many surgical procedures can produce undesirable side effects. Individual women and practitioners will place different values on the various outcomes presented to them when choosing between caesarean section and labour. Women may choose caesarean section because they wish to protect the pelvic floor to prevent urinary problems in the future.[13] However, a lack of consensus exists about childbirth induced trauma of the pelvic floor and the extent to which short or longer term urinary or faecal problems can be prevented by caesarean section.[13 14] Thus, women and their care providers are left uncertain about the benefits of caesarean section when weighed against the potential harms. Women with no other indication for caesarean section would need to weigh up the possible but uncertain benefit of preventing urinary problems in the future against the increased chance of problems related to surgery in themselves or their baby.

Judgment about which method of birth is best depends not only on the relative odds of experiencing a large range of benefits and harms, but also on their relative size or severity. When comparing caesarean section with labour, it is crucial to ascertain the probability of experiencing the various options for mode of birth once labour starts (normal vaginal birth, instrumental vaginal birth, or intrapartum caesarean section), given that the resulting health of mothers and babies will differ depending on whether or not normal vaginal birth is achieved. The probabilities of various birth outcomes and the resulting health of both the mother and baby rest heavily on a range of decisions made before and during labour. For example, decisions about interventions such as induction of labour and use of epidural for pain relief can increase the likelihood of surgery.[15] Mode of birth also depends upon consumer preferences, type of practitioner (midwife or obstetrician), birthing environment (hospital or home), and healthcare funding structures (health insurance and financial incentives).

Because of the complex nature of decisions about mode of birth, its sociopolitical context, and the uncertainty about outcomes, randomised controlled trials are unlikely to provide definitive answers for women and their care providers about which mode of birth is best for them. Cohort studies may provide more accurate estimates of risk factors for mode of birth when the complex relations between process factors such as induction of labour, epidural pain relief, type of practitioner, and funding arrangements are modelled as endogenous rather than exogenous variables in the analysis. Future work should help to establish a consistent set of probabilities for the range of outcomes according to these factors, to support practitioners who guide and inform individual women's birth decisions. Exploring models of pregnancy and childbirth care that provide the best birth outcomes as well as supporting birth environments and practices that complement rather than counteract the normal physiology of childbirth is imperative.

All references are in the version on bmj.com

Management of community acquired pneumonia

New studies assess the effectiveness of vitamins for prevention and initial antibiotic coverage for atypical pathogens

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Research into community acquired pneumonia has traditionally focused on prognosis and on finding the most effective antibiotic treatment. Little attention has been paid to identifying risk factors for this disease, particularly modifiable ones.

A recent prospective cohort study conducted within the nurses' health study II measured the effect of dietary and supplemental intake of individual vitamins on the incidence of a first case of community acquired pneumonia in otherwise healthy well nourished women.[1] The participants were 83 165 nurses aged 27-44 in 1991. Dietary information and the occurrence of community acquired pneumonia were assessed every four years through a semi-structured questionnaire. The diagnosis was confirmed by a chest radiograph.

On the basis of 10 years of follow-up and 925 new cases of community acquired pneumonia—and after adjusting for age, body mass index, smoking status, alcohol use, physical activity, and total energy intake—no overall association was found between dietary and supplemental intake of individual vitamins and the incidence of the disease. Subgroup analysis hinted at a possible protective effect of high dietary vitamin E intake in smokers who did not take vitamin E supplements, but overall the study adds to the small amount of evidence indicating that high vitamin intake by well nourished healthy adults does not protect against community acquired pneumonia.

With regard to treatment, the need to cover for atypical pathogens (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*) when initially treating community acquired pneumonia in hospital is controversial. Some guidelines (from Canada, Germany, Japan, parts of Latin America, the United Kingdom, and the United States) advocate atypical

coverage,[2-7] while others (from France, Hong Kong, Saudi Arabia, and South Africa) consider it optional.[8-11] These discrepancies are largely the result of two unresolved matters—lack of knowledge about the incidence of atypical pathogens as a cause of community acquired pneumonia worldwide and uncertainty about the effect of atypical coverage on clinical outcomes.

A recent study attempted to look at both problems by analysing data from two international databases—the reference laboratory database for atypical pathogens at the University of Louisville and the community acquired pneumonia organisation (CAPO) database.[12] The first of these databases contains data on 4337 patients (from 21 countries) with a laboratory diagnosis of atypical pneumonia. The data were collected during phase III clinical trials of antimicrobials against community acquired pneumonia, carried out by Abbott, Pfizer, and Bristol-Myers Squibb from 1996 to 2004. The CAPO database contains retrospectively collected data (obtained by chart abstraction) on the management of community acquired pneumonia in 2878 patients admitted from 2001 to 2006 to 39 hospitals in 11 countries. Atypical coverage was defined as any antibiotic regimen containing a macrolide, a tetracycline, or a fluoroquinolone. The main clinical outcomes were time to clinical stability, length of hospital stay, total mortality, and mortality related to community acquired pneumonia.

In the University of Louisville database, 22% of patients worldwide tested positive for atypical pathogens. Regional figures ranged from 20% in Asia and Africa to 28% in Europe, with 21% in Latin America and 22% in the US and Canada. The CAPO database showed large variations in the proportion of patients in hospital who were initially treated with a regimen covering atypical pathogens. The figures varied from 91% in the US and Canada to 10% in Asia and Africa, with Europe (74%) and Latin America (53%) lying in between; the global average was 77%. After controlling for factors such as severity of illness and process of care (but not geographical region), patients with atypical coverage were more likely to be clinically stable within one week (hazard ratio 1.26, 95% confidence interval 1.13 to 1.41); they also had decreased total mortality (7% *v* 11.1%; adjusted odds ratio 0.54, 0.42 to 0.71) but not decreased mortality related to community acquired pneumonia (3.8% *v* 6.4%; adjusted odds ratio 0.79, 0.52 to 1.21) compared with those without atypical coverage. The administration of antibiotics within eight hours of admission significantly reduced total mortality (odds ratio 0.57, 0.44 to 0.74). The lack of multivariate control for geographical region is unfortunate—residual confounding as a result of this and other undocumented factors may partially explain the results. However, control for severity of illness partially compensates for this.

This study adds to the evidence indicating that initial coverage for atypical pathogens may reduce total mortality.[12] Although some studies have shown no reduction in total mortality, this study indicates that the choice of initial antibiotic in adults admitted to hospital probably has a direct effect on patient outcomes. Consequently, it would be advisable to switch to or add an antibiotic that covers atypical pathogens in patients not initially covered for atypical pathogens who do not improve within two to three days of treatment. The extent to which this applies to the initial treatment of ambulatory patients is not clear, but a high degree of suspicion is warranted.

It remains to be seen whether the evidence from this study will affect guidelines that do not advocate initial coverage for atypical pathogens. The recently updated guideline of the Infectious Diseases Society of America continues to recommend antibiotic regimens offering atypical coverage as initial treatment of both inpatients and outpatients with community acquired pneumonia.[3] The only substantial change in terms of antibiotic regimen is the mention of ertapenem as an alternative to beta-lactams for selected patients. Otherwise, the guideline emphasises problems within the process of care and how diagnostic testing can alter management; it also recommends that antibiotics should be started while patients are still in the emergency department. Immunisation against influenza and pneumococci, smoking cessation, and respiratory hygiene measures are also dealt with. Overall, the guideline provides a wealth of information for clinicians involved in the acute care of patients.

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Timing of surgery for inflammatory bowel disease

Thresholds for elective surgery may be too high

RESEARCH, p 1033

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In this week's *BMJ*, Roberts and colleagues used record linkage analysis to compare mortality rates after elective colectomy, emergency colectomy, and no colectomy in people admitted with inflammatory bowel disease.[1] The results are important and indicate that thresholds for undertaking elective colectomy in clinical practice are too high.

The chronic inflammatory bowel diseases—ulcerative colitis and Crohn's disease—affect 1.4 million people in the United States and 2.2 million people in Europe.[2] They result in substantial morbidity, lost days at work, and reduced quality of life. Despite a variety of advances in medical treatment, 20-30% of patients with ulcerative colitis need surgery at some time,[3] while the lifetime risk of surgery for Crohn's disease is as high as 80%.[4] In people with severe inflammatory bowel disease the long term effectiveness of drugs, such as immunomodulators, rarely exceeds 40%. Surgery can be regarded as a cure for ulcerative colitis, albeit an imperfect one. Similarly, surgery can be highly effective in Crohn's disease but is offset by the recurring nature of the disease.

The lack of consensus on how to manage these patients means that doctors and surgeons spend much time debating the optimal timing of surgery. In general, surgery is undertaken to improve symptoms and quality of life, to offset or resolve complications (such as abscess or perforation), or for the salvage of acute severe disease. Although gastroenterologists know the potential complications associated with acute severe disease, most are reassured by overall mortality data, which consistently show that people with inflammatory bowel disease have near normal standardised mortality ratios. A prospective cohort of 692 people with inflammatory bowel disease in Olmsted County, Minnesota showed an overall standardised mortality ratio of 0.8 (95% confidence interval 0.6 to 1.0) for ulcerative colitis and 1.2 (0.9 to 1.6) for Crohn's disease over a 44 year follow-up.[5] A European cohort of 796 patients with the disease across 10 centres in north and south Europe showed a standardised mortality ratio of 0.69 (0.21 to 0.91) for men with inflammatory bowel disease and 1.18 (0.54 to 2.25) for women.[6] In a 10 year follow-up of the same cohort, 8.7% underwent colectomy. Interestingly, wide differences in colectomy rates were seen between north and south Europe (10.4% *v* 3.9%; P<0.001).

Despite these reassuring statistics, Roberts and colleagues' findings appear alarming at first glance. In England and Wales between 1998 and 2000, three year mortality for a general admission to hospital was 12.2% (11.5% to 12.9%) for ulcerative colitis and 9.1% (8.5% to 9.7%) for Crohn's disease. For ulcerative colitis, three year mortality was much higher for emergency operations (13.2%, 11.0% to 15.8%) than for elective operations (3.7%, 2.7% to 4.9%).

Although these figures seem high, they cover a three year period, and the one month mortality figures for elective and emergency operations of 0.8% and 5.7% are similar to other published studies. Perhaps most worrying is the mortality in people admitted for ulcerative colitis and Crohn's disease who had no surgery (13.6% (12.8% to 14.5%) and 10.1% (9.4% to 10.8%)). Most deaths occurred after the acute admission—more than half occurred between six and 36 months later. Unfortunately, because of the nature of the study, exactly how these patients died is not clear.

The recent national inflammatory bowel disease audit (a collaboration of the British Society of Gastroenterologists, Royal College of Physicians, National Association for Colitis and Crohn's Disease, and Association of Coloproctology of Great Britain and Ireland) gives some additional information about cause of death in patients with inflammatory bowel disease.[7] The audit documents 2767 admissions for ulcerative colitis, of which 397 were elective. Forty five patients (1.6%) died in hospital—25 deaths were directly attributable to ulcerative colitis—and operative mortality was 2.1% (15/715). A further 47 deaths (mortality of 1.7%) occurred after discharge, in a median follow-up period of 80 days; only eight (17%) were attributed to ulcerative colitis. In Crohn's disease 2914 patients were admitted, 556 for elective surgery; 36 (1.2%) died in hospital, 25 as a direct result of Crohn's disease. Operative mortality was 1.2% (14/1092), and 36 people died after discharge (mortality of 1.2%), only 13 (36%) as a direct result of Crohn's disease. Although the audit had a shorter follow-up than that used in the paper by Roberts and colleagues, and mortality may have been under-reported because of difficulty in retrieving notes, these unadjusted mortality figures are reassuringly closer to those reported in the above cohort studies.

Roberts and colleagues infer that people with inflammatory bowel disease who have planned elective surgery fare much better than those in hospital for emergency treatment. This may be true, but it does not follow that patients having elective surgery would otherwise end up in hospital for intensive medical treatment or emergency surgery. Equally, patients having emergency treatment may have had no previous opportunity for elective treatment.

Are there missed opportunities for elective surgery in the emergency admission group? The decision to operate remains a difficult one, that should involve the doctor, surgeon, patient, and family. Decision making is not helped by the lack of clear data on surgical outcomes. The idea that surgery for inflammatory bowel disease should be the last resort is flawed, and the data presented by Roberts and colleagues—even allowing for interpretation—should be a word of caution to those who promote it.

All references are in the version on bmj.com

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