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On the road: accidents that should not happen

If you are aged 15–19 years old, what is your most likely cause of death at that age? AIDS? Tuberculosis? Suicide? All likely suspects, but the answer is death in a road-traffic accident. Such a fate is the second most likely cause of death in the 5-year age-bands above and below 15–19, and the third most likely cause in those aged 5–9 years, according to *Youth and road safety*, a report by WHO that will be released on April 23. Most victims will be young men and boys. Men aged under 25 years are nearly three times as likely as women of that age to be killed in a road-traffic accident.

The first weeks of April have been typical for death and injury on the road. In Induruwa, Sri Lanka, a truck and bus collision killed 23 people. In Islamabad, Pakistan, a truck killed four family members, including two children, when it crashed into a bus stop. In Tangail, Bangladesh, a cement truck crashed, killing nine people travelling onboard. During the first 2 days of the Thai New Year holiday, 98 people died in traffic accidents, and over 1300 were injured. In Los Angeles, USA, film director Robert Clark died with his son in a head-on crash with a vehicle driven by a drunken driver. On April 13, Jon Corzine, Governor of New Jersey, was seriously injured when his car was hit by a pickup truck. Those glimpses from news reports, particularly the anonymous reports from poorer countries, highlight where the problem is worst. In 2002, of over 380 000 deaths in road-traffic crashes, half were road users from Africa and southeast Asia.

The launch of *Youth and road safety* coincides with the start of the first UN Global Road Safety Week, which follows on from the World Health Day in 2004 that was called "Road safety is no accident", a slogan that is being re-used for the current campaign. An accompanying report, *Faces behind the figures: voices of road traffic crash victims and their families*, tells the stories of accident victims and their families and friends.

Statistics from *Youth and road safety* are chilling. During the upcoming road-safety week, about 7000 people aged under 25 will be killed in a road-traffic accident. Yearly, 1·2 million people around the world die in road-traffic accidents, with millions more being injured. The most common cause of death is, unsurprisingly, traumatic brain injury. The consequences of a road-traffic accident are not just for health. Each year, road crashes in low-income and middle-income countries cost US$65–100 billion which, as the report points out, is more than the total annual development aid given to those countries. The economic burden is not restricted to poor countries. In 2002, the latest year for which figures are available, road-traffic crashes involving 15–20-year-old drivers cost the USA $41 billion. When a young person is injured in a road-traffic crash, especially if the injury causes chronic disability, their lifelong earning capacity can disappear, their education can be ended or interrupted, or their family has to take on the burden of caring for them.

What is it about young people on the roads, especially young men, that puts them at such high risk? In low-income and middle-income countries, the casualties are more likely to be pedestrians, cyclists or motorcyclists, or passengers, mostly because, in such countries, the transport and urban infrastructure is not geared up to non-motorised road users who have to share road space with cars, buses, trucks, and animals. Also, pedestrians rarely wear protection such as bright, fluorescent, or reflective clothing. Young road users are at risk because of drinking alcohol, driving too fast, and being an inexperienced driver. They can also be insufficiently mature developmentally to understand risks on the road, or to predict or react to complex traffic situations. They are sometimes loathe to wear seat-belts or helmets, and can be unduly influenced by peers to take risks or even actively follow risky behaviour.

Death and injury on the road is a pandemic, especially in young people. Road planners can make a difference, by building in traffic-calming measures and separating motorised vehicles from pedestrians and cyclists. The police can make a difference by enforcing road-safety laws, particularly those to do with driving under the influence of alcohol, and the wearing of helmets. There are even innovations such as graduated driving licences for young people in which the learner period is lengthened and restrictions are put on carrying passengers.

But the individual solution lies with what is perhaps one of the hardest things to change—human behaviour. Road accidents disproportionately affect young people. Being taught about road safety from a very young age must become a priority, with adults setting a good example at all times. ■ *The Lancet*

For more on the **UN Global Road Safety Week** see http://www.who.int/roadsafety/week/en/index.html

Australia: the politics of fear and neglect

PA

Australian clinical and public-health research is an emblem of excellence across the Asia-Pacific region. That enviable position is being put at risk by Prime Minister John Howard's indifference to the academic medical community and his profound intolerance to those less secure than himself and his administration. The latest example of his complacency was a comment he made on a Melbourne radio station last week. He said that people living with HIV should not be allowed to enter and live in Australia—"prima facie, no", he asserted. Australia already has tough immigration rules for those with HIV. All hopeful migrants aged over 15 years are tested for the virus. Their applications stumble if they are found to be positive.

To any visitor, Australian culture feels progressive and inclusive. This attractive exterior belies a strong undercurrent of political conservatism, which Howard is ruthlessly tapping into. As the Australian columnist Janet Albrechtson wrote recently, "the Australian polity is inherently conservative…a conservative coalition has ruled for 42 of 58 years". 2007 is an election year for Australia. How the country interprets its past and sees its hopes for the future will be critical not only for the health of its people but also for the contribution Australia makes to world health. At present, Australian politicians are scoring well below their potential.

Take Aboriginal health. The current health minister, Tony Abbott, recently insulted Aboriginal peoples by claiming that those who spoke up for indigenous health were simply "establishing politically and morally correct credentials". On climate change, environment minister Malcolm Turnball apparently sees little new in the latest alarming assessments by the UN's Intergovernmental Panel on Climate Change.

Reviewing the effect of successive Howard administrations on Australia's academic community since 1996, the respected scientist Ian Lowe has written that "the present government has gone to extraordinary lengths to silence independent opinion within the research community". This year provides an opportunity at the ballot box to bring a new enlightenment to Australian health and medical science. ■ *The Lancet*

Improving access to second-line antiretrovirals

Still Pictures

In June, 2006, UN member states at the High Level Meeting on AIDS committed themselves to provide universal access to comprehensive prevention programmes, treatment, care, and support by 2010. This week WHO, UNAIDS, and UNICEF publish the first report about progress towards this goal. Sadly, there is little for the international community to be pleased about. Although 2 million people had access to antiretroviral therapy at the end of 2006, 5 million were still in need of treatment.

Some progress has been made in reducing the costs of first-line antiretrovirals. In low-income and middle-income countries the prices of most first-line drugs decreased by between 37% and 53% from 2003 to 2006, contributing substantially to the wider availability of treatment. But more patients put on treatment will inevitably be accompanied by increasing HIV-drug resistance. Second-line drugs, and new types of antiretroviral drugs in the future, such as the integrase inhibitors, have the potential to offer new treatment options for patients whose disease no longer responds to first-line drugs. But unless prices for second-line regimens fall substantially, budgetary constraints mean treatment programmes will be put at risk.

Last week, Abbott Laboratories announced plans to reduce the cost of its second-line drug lopinavir/ritonavir in 40 low-income and middle-income countries, following a meeting with WHO Director-General, Margaret Chan. But the meeting only took place after advocacy groups pressured WHO to take a strong line with Abbott over its aggressive pricing policy for lopinavir/ritonavir and its continued stance in not registering new drugs in Thailand, after the Thai Government issued a compulsory licence for lopinavir/ritonavir.

WHO can do more. Developing a robust plan on access to second-line drugs in collaboration with its partners, as called for by the International Treatment Preparedness Coalition—a worldwide group of people living with HIV/AIDS and their advocates—would be a good start. Such a move would show that WHO is serious about defending the interests of patients with HIV/AIDS. ■ *The Lancet*

For the report ***Towards universal access: scaling up priority HIV/AIDS interventions in the health sector*** see http://www.who.int/hiv/mediacentre/univeral_access_progress_report_en.pdf

For more on **integrase inhibitors** see **Comment** *Lancet* 2007; **369:** 1235 and **Articles** *Lancet* 2007; **369:** 1261–69

For more about the **International Treatment Preparedness Coalition** see www.aidstreatmentaccess.org

For more on **WHO and the Abbott case in Thailand** see **Comment** *Lancet* 2007; **369:** 974–75

Global poliomyelitis eradication: status and implications

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The Global Polio Eradication Initiative (GPEI) is among the most ambitious programmes ever undertaken by WHO. Begun in 1988, it has made extraordinary progress, reducing the global incidence of poliomyelitis by more than 99%.[1,2] Wild poliovirus is now regarded as endemic in only four regions of the world. In Afghanistan and Pakistan, security problems have hampered vaccine delivery. In northern Nigeria, there has been a loss of public confidence in the vaccine, low uptake, and consequent outbreaks which have seeded virus into several other countries. And in the Indian states of Uttar Pradesh and Bihar, the wild virus has proven extraordinarily well entrenched, partly because of low efficacy of conventional trivalent oral poliovirus vaccine (tOPV) in that environment.[3] Other problems have arisen that could threaten the feasibility of stopping all poliovirus transmission: the recognition of circulating virus derived from oral vaccine,[4] persistent excretion of poliovirus by immunodeficient individuals,[5] and difficulties in ensuring containment of all potential sources of reintroduction.[6] These difficulties have led to a recommendation that the programme abandons its eradication goal in favour of a control approach.[7] Two papers in today's *Lancet* provide important perspectives on this debate and on the current stage of the programme.

Nicholas Grassly and colleagues analyse recent data from India to compare the effectiveness of a monovalent oral type 1 poliovirus vaccine (mOPV1) with that of tOPV.[8] There are problems in inferring absolute vaccine efficacies in such circumstances. But the relative efficacy estimates should be valid, and they indicate that the newer mOPV is more effective than the older tOPV. Let us hope this difference is sufficient to terminate the remaining chains of transmission of type 1 wild poliovirus.

Kimberly Thompson and Radboud Duintjer Tebbens use a dynamic model to show that a decrease in immunisation intensity in endemic areas will result in a rapid accumulation of susceptible individuals and many more cases of paralytic poliomyelitis (northern India is used as an example).[9] In addition, they argue that both the cumulative number of patients with paralytic poliomyelitis, and the financial costs, that would occur with various control options are higher than with any of four policies suggested for the era after "poliomyelitis eradication" (defined by these authors as interruption of wild virus transmission). The cost difference between the posteradication and control scenarios is used to conclude that "we should be willing to invest more than $8000 million to achieve eradication". The authors conclude that even a policy that included global introduction of inactivated poliomyelitis vaccine (IPV) after the "eradication" of poliomyelitis will, over 20 years, cost less than implementing any of the modelled control strategies. Readers may note that Thompson and Duintjer Tebbens' use of the phrase "poliomyelitis eradication" for interruption of wild poliovirus transmission is confusing, and exacerbates a semantic problem which has haunted the GPEI since its inception. The termination of wild virus transmission does not guarantee eradication of poliomyelitis disease, considering that OPV viruses are transmissible and are known to revert back to wild-type phenotype.[4,10] WHO has recognised this problem and declared that OPV will have to be discontinued if poliomyelitis is to be eradicated.[1,2] The essential step of terminating transmission of all OPV-derived viruses remains untested.

These two papers provide encouraging insights into the current methods and long-term economics of the GPEI. The demonstration of superior effectiveness of mOPV vaccine adds to the evidence that termination of wild poliovirus transmission is technically feasible, given enough time, continued funding, political stability, and continued political support in the affected areas of the world. The modelled illustration of the financial

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Coloured transmission electron micrograph of polioviruses

implications of managing patients with paralytic poliomyelitis and continuing to control poliovirus with supplemental immunisation activities is based on a large number of assumptions, but it supports arguments against abandoning the goal to eradicate wild virus at least.

Despite its established efficacy against wild virus, the usefulness of mOPV in combating transmission of vaccine-derived viruses, after the eradication of wild virus, is unclear. Such future use of this vaccine implies fighting fire with fire, with the risk of seeding additional live viruses into the population.[11] As of now, the only other available technology to help curtail transmission of OPV-derived viruses is IPV; but this use of IPV has yet to be assessed in the difficult areas of the world. IPV should at least help (IPV has been sufficient to arrest transmission of all polioviruses in several countries with high levels of hygiene), but only if used at coverage levels which are far higher than currently achieved in several of the poorest countries of the world. The needs of the GPEI might thus become coincident with those of the GAVI Alliance, which has set a target of 90% routine vaccine coverage in low-income countries by 2010.[12] This sharing of interests could prove a powerful lobby for public health. A world in which all children, everywhere, receive all the recommended vaccines could and should be among the legacies of the programme that was started to eradicate poliomyelitis.

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Surveillance of acute flaccid paralysis in India

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Poliomyelitis eradication requires surveillance for acute flaccid paralysis (AFP), and in all countries children with AFP who are younger than 15 years are investigated for poliovirus in stool. However, collection of two 8-g stool samples 24 h apart and within 14 days of onset of paralysis is not easy. Samples need to be stored below 8°C, documented properly, and tested in an accredited laboratory.

Individuals without adequate stool samples are examined by a neurologist with electromyography and nerve-conduction and other tests. A national expert committee[1] reviews these cases, decides whether any are poliomyelitis, and labels them as compatible poliomyelitis in accordance with WHO's recommended virological classification scheme.[1,2] The occurrence of compatible poliomyelitis suggests a failure of the surveillance system.[3]

Poliomyelitis eradication in India is a huge challenge. The National Polio Surveillance Project,[2] established in India in 1997 to guide public-health experts, has been a successful model for surveillance activities globally. In India, it was hoped that poliomyelitis would be eradicated quickly, but the virus resurged in 2006. It seems that India did everything according to the surveillance rulebook.

To avoid missing cases of paralytic poliomyelitis, the prevalence of non-poliomyelitis AFP should be at least 1 per 100 000 in children younger than 15 years. To ensure that we identify the virus, 80% of AFP cases should have adequate stool samples. If these criteria are met and no cases of poliomyelitis are identified for 3 years consecutively, we can conclude fairly certainly that the country is free of poliovirus. However, if the

frequency of adequate stool samples is 80%, then 80% of all poliomyelitis cases must be confirmed. India had certification-quality surveillance for the past 8 years. The prevalence of non-poliomyelitis AFP, which had been 2 people in 100 000 since 1998, increased in 2004 to about 3 in 100 000 and approximately tripled in 2006 to 6·95 in 100 000.[2,4]

The number of confirmed poliomyelitis cases has declined since 1998, except during outbreaks in 2002 and 2006. In 2005, we hoped that we had finally conquered the virus. However, the virus made a comeback. The worst affected area was Uttar Pradesh, which consistently had the maximum number of poliomyelitis cases. Why did poliomyelitis eradication fail? A key issue is hidden in AFP data. Although India achieved the recommended surveillance indicators, there was a serious anomaly: the number of compatible poliomyelitis cases had always been more than 20% of total cases.[4] The lowest frequency (30%) of compatible poliomyelitis cases was achieved in 2002, the year with the biggest outbreak; and the proportion of compatible cases had been increasing as the number of confirmed poliomyelitis cases decreased.[4]

The 2005 data in the worst affected states of the 2006 outbreak—Uttar Pradesh and Bihar—highlight this anomaly (table).[2] The frequency of non-poliomyelitis AFP is high in Uttar Pradesh and Bihar, 13 times more than expected.[2] Although the frequency of non-polio AFP in Uttar Pradesh was very high and the frequency of adequate stool samples was more than 80%, the proportion of compatible cases was more than 80%. Because the number of compatible poliomyelitis cases should be less than 20%, India has missed many cases over the past several years, which has adversely affected efforts to eradicate the virus. This situation seems to be an inadvertent but tragic consequence of reliance on only two indicators to assess the quality of AFP surveillance. By contrast, surveillance data for Indonesia in 2005 show that the proportion of compatible poliomyelitis cases from the total was about 20% (75 compatible cases and 349 confirmed cases).

	Uttar Pradesh	Bihar	National
Non-poliomyelitis AFP (in 100 000)	13·85	14·02	6·43
Proportion with adequate stool	82%	81%	81%
Total poliomyelitis cases	209	136	463
Confirmed poliomyelitis cases	29	30	66
Number of compatible poliomyelitis cases (% total poliomyelitis)	180 (86%)	106 (78%)	397 (86%)

Table: **AFP surveillance indicators and poliomyelitis cases in India and for Uttar Pradesh and Bihar,[2] 2005**

The aim of AFP surveillance is to detect circulating poliovirus through identification of paralytic poliomyelitis cases. Using only two essential criteria for maintaining the quality of AFP surveillance has failed in India. A third factor should be added to the criteria for quality surveillance—the proportion of compatible poliomyelitis cases among the total poliomyelitis cases should not exceed 20%. This new criterion would check the reported frequency of adequate stool samples. However, the 20% threshold should be reduced proportionately if the prevalence of non-poliomyelitis AFP is much higher than 1 in 100 000 to avoid a false sense of increased surveillance quality.

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Limits of substance-use interventions in developing countries

As part of the *Lancet* Series on adolescent health, John Toumbourou and colleagues[1] review the efficacy and effectiveness of approaches and strategies designed to prevent substance use and reduce substance-related harm in young people. The authors address an important public-health and welfare issue, one that has attracted much attention from professionals and policymakers in industrialised countries for decades, and is increasingly being recognised as a problem in low-income and middle-income countries.

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Panos Pictures

Homeless boy sniffing glue in Thailand

Toumbourou and colleagues provide a good summary of the risks associated with harmful use of alcohol and drugs, drawing largely from work done within the WHO Global Burden of Disease project, to which some of the coauthors contributed. Probably the most relevant finding of this project was one reported in the World Health Report of 2002, that addictive behaviours are among the top ten contributors to global disease burden measured in disability-adjusted life-years.[2] In fact, alcohol was shown to be the leading risk factor and tobacco came third in developing countries with rising economic prosperity. This work and growing evidence have shown that what was seen by many in developing countries as a disease of industrialised nations is now a worldwide trend. Not only are increasing numbers of young people in these mostly poor countries resorting to licit and illicit drugs for recreation and excitement, but problems associated with use are also on the rise.

Yet, as Toumbourou and colleagues recognise, it is a challenge trying to make sense out of what is going on in all but a few countries. Indeed, it has become customary to bemoan the underdeveloped state of knowledge in almost every field in these countries,[3] a situation that has made it difficult, and certainly unwise, to be too inclusive in our generalisations about global problems and how to address them. Such generalisations would be particularly suspect when dealing with a problem in which cultural underpinnings and the political climate have substantial roles.

That is the basic difficulty facing Toumbourou and colleagues—the current state of knowledge about the extent of adolescent substance use, and what works in reducing problems, is restricted to knowledge from a few high-income countries.[4,5] And so the authors work with what they have and rely on studies and trials done in just a few countries and published in a small band of English language journals. Even their introductory section on the epidemiology of drug use relies on the European school survey, the US Monitoring the Future project, and a study in Australia.

The inherent limitation of a review that does not include the experiences of the great majority of adolescents in the world today is magnified when the topic is the efficacy or effectiveness of interventions. Though one can argue that knowledge about substance use in young people in some developing countries is growing, the same cannot be said for studies (controlled or not) that test the efficacy of interventions. Such investigations are indeed scarce, but another problem is access to existing work if the papers are published in national or regional journals not included in indexing services. So, although more representative studies are obviously needed from the world outside the USA, Canada, Europe, and Australia, we also have to find ways of going beyond the narrow confines of scientific publications as determined by these sources to discover what else might be available out there. The internet means this move is easier to make today than it would have been even a decade ago.

Finally, although developing countries have something to learn from the experiences of industrialised countries, success in preventing substance use and reducing related problems in these countries will come not in the application of any one strategy or group of strategies but by addressing the issue within the broad context of development planning.[6] These, after all, are countries faced with the reality of poverty; where drug policy is often limited to law enforcement, prevention is sporadic and left to the goodwill of individuals and non-profit groups,[7] resources are limited, and drugs and alcohol problems compete with what policymakers might regard as more immediate problems of survival.

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Morphine kills the pain, not the patient

Just over 20 years ago, John Morgan,[1] an American pharmacologist, coined the term opiophobia to describe the analgesic-prescribing habits of physicians he had studied. Then, in 1987, WHO published its analgesic ladder,[2] which identified morphine as the most effective analgesic for cancer pain and effectively made a nation's per-capita consumption of morphine a proxy for the extent to which its citizens have access to pain relief and palliative care. Global morphine consumption has risen from 3·3 tonnes in 1985, before WHO's intervention, to 28·7 tonnes in 2004.[3]

However, underneath this change in prescribing practice, professional and public anxieties about the effects of morphine continue to hinder adequate access to analgesia. The best-known fact about morphine among the public and physicians is that it can be addictive (in fact the risk of iatrogenic addiction is under 0·01%[4]). For physicians, the second best-known fact is that morphine can precipitate respiratory depression. As a consequence, if offered enough confidentiality, clinicians can readily be found who will confess to having shortened the life of their patients to achieve pain control.[5] Harold Shipman's use of morphine as his murder instrument has further increased disquiet among UK medical professionals and laity. Therefore, that the media take it as an accepted fact that everyday medical practice for pain control entails the use of increasing morphine doses until the patient dies as a result is unsurprising.[6] This is a taint to which physicians specialising in pain management and, particularly, palliative care have been obliged to become accustomed.

The recent study from the US National Hospice Outcomes Project, which compared opioid use and survival at the end of life, is thus welcome,[7] as it represents the largest and most sophisticated examination of the issue to date. In 725 hospice inpatients with end-stage cancer, lung disease, or heart disease who were followed up until death, length of stay was positively correlated with the maximum daily opioid dose received, even when that dose exceeded 1·8 g a day—around 15 times the average for such patients in the UK and Japan.[8,9] Neither absolute nor percentage change in dose was linked with survival. In fact, multivariate analysis found no combination of factors capable of explaining more than 8% of the variation in survival time, which suggests an overwhelming influence of the individual's disease severity.

A systematic review of previous (albeit smaller) studies, from palliative-care services in various countries, found no significant difference in survival according to either absolute morphine dose or change in morphine dose.[10] These results are consistent with widespread clinical experience with morphine for analgesia. Only the opioid-naive patient is at significant risk of respiratory depression.[11] A patient with moderate-to-severe chronic pain, whether malignant in origin or not, who is given the incremental dose-titration practised in pain and

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Opium poppy

palliative care centres is not at such risk. A physician who truly is killing his or her patient in the name of pain relief is not merciful, just incompetent.

What renders the situation frustrating is that the perception otherwise is so hard to shift. This problem matters because underprescribing of opioids remains a major barrier to effective pain control.[12] Furthermore, if ineffective pain management is still an issue in high-income countries, it is nearly universal in low-income countries where access to morphine is limited or absent, but where most people dying from cancer or AIDS reside.[13] Governmental fears of illicit trafficking of morphine are part of the problem, but so are medical anxieties about adverse effects. The opiophobia that disallows all opioid drugs can change specifically into morphine phobia, with the result that only expensive alternative opioids, albeit with the same potential side-effects,[14] are allowed. Either way, the poor get nothing. Yet morphine, properly used, is safe, and 10 mg should not cost more than one US cent.

As Portenoy and colleagues[7] remark, "the timing of death in…far advanced illness involves a complex interplay of variables, and opioid therapy should not be the focus of future research of this type…Physicians should be encouraged to use opioids effectively to relieve suffering at the end of life." Let's move on, everyone.

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Give a drug a good name

"Dear doctor…I note your patient has been taking chlorampicillin for several months. I found no infection and have asked her to stop taking it." The doctor who dictated this letter confused chlorampicillin with chlorambucil. Drug names are not always easy to differentiate, and serious errors can occur.[1] However, the naming of medicines is not straightforward.

There are several national and international naming schemes. The best known are the British Approved Name (BAN), dénomination commune française (DCF), Japanese Accepted Name for Pharmaceuticals (JAN), and US Adopted Name (USAN). National schemes require manufacturers to use the approved name. In many countries, the approved name has to be used on prescriptions and labels of dispensed medicines.

National bodies such as the British Pharmacopoeia Commission and the USAN Council contribute to WHO's panel of international nomenclature experts on recommended International Non-proprietary Names (rINNs).[2,3] Occasionally, an objection is raised to a name and if agreement cannot be reached, the name remains a proposed INN (pINN). For example, amantadine was proposed in 1965,[4] but it has not become a rINN because an objection remains on file. In practice, this is not problematic because amantadine is the BAN, DCF, JAN, and USAN.

Although close involvement of national bodies in the coining of INNs has aided international standardisation, approved names sometimes differ between countries. To harmonise names in Europe, the Council of the European Communities requires the so-called common name on medicine labels.[5] According to directive (92/27/EEC), the common name means the rINN or, if one does not exist, the usual common name.

In the UK, after a faltering start, the few BANs that were not rINNs were changed except, for good reasons,[5]

adrenaline and noradrenaline (rINNs epinephrine and norepinephrine, respectively). Holders of marketing authorisations for the drugs affected by the harmonisation procedure were asked to change to the new BANs by December, 2004. Manufacturers' product literature that made incidental reference to an old name was to be changed by December, 2005. Despite the European directive, some rough edges remain. Whereas the European Pharmacopoeia uses deferoxamine, the BAN is desferrioxamine. Deferoxamine is a pINN and is therefore outside the scope of the directive.

Consideration of an INN is triggered most commonly by an application from a manufacturer to WHO,[3] and is commonly submitted through the competent national body, usually when the pharmacology and potential clinical benefit of the candidate substance are known. The application will generally include one or more suggestions for the INN. Working to guidelines developed for the construction of INNs, WHO's expert panel selects a name suggested by the applicant or an alternative if the suggested name is unsuitable. The pINN is published, and if no objections are raised within 4 months the name is adopted as the rINN.

INNs have to be short, recognisable when written and spoken, and unlikely to be confused with other commonly used names.[6] Substances with the same action or structure have a common segment (a stem) in their names—ie, a suffix, prefix, or midsegment.[7] For example, the INNs for antagonists of angiotensin II receptors include the stem "-sartan", and the stem "vin-" suggests a vinca alkaloid. Several stems can be combined: monoclonal antibodies, which end in "-mab", contain two other stems to reflect the target and the method of raising the antibody;[8] and "vir" (ie, antiviral) can be combined with other stems, as in "-amivir" (neuraminidase inhibitors) and "-cavir" (carbocyclic nucleosides).

Sometimes, improved understanding of a compound's pharmacology or a new therapeutic use makes the assigned stem no longer appropriate. For years, the INN amfebutamone suggested kinship with amfetamine, but the name was changed to bupropion, because of the distinct pharmacology of bupropion compared with amfetamine. Furthermore, the INN should be usable in as many languages as possible (eg, the letters h, k, ae, and oe are avoided; the letter f is used instead of ph, and i is used instead of y). Older names might be inconsistent, but newer names obey these rules.

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There are rules for the coining of proprietary names. For example, resolution WHA46 of the World Health Assembly states that trademarks should not be derived from INNs, and that INN stems should not be used in trademarks.[7] Furthermore, guidelines from the European Medicines Agency[9] state that the invented name of a medicinal product should not: convey misleading therapeutic or pharmaceutical connotations; mislead about the product's composition; or cause confusion with the name of an existing medicine when spoken or written. The revised version of these guidelines is scheduled for publication in June, 2007.

Despite the care taken over the naming of medicines, mistakes occur. For example, when BANs became identical with rINNs, there was confusion between new and old names. Mercaptamine (previously cysteamine) was confused with mercaptopurine, and levothyroxine (previously thyroxine) was confused with liothyronine. Over time, such errors should become less common, but new names give scope for new errors.

Incidentally, the patient mentioned in our opening paragraph continued to take chlorambucil—her GP knew that there is no such drug as chlorampicillin.

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Frailty in elderly people

The number of elderly people is increasing worldwide, and their autonomy and wellbeing is important. By reaching the limit of the human lifespan, centenarians give valuable clues about mechanisms of successful ageing. The Japanese Centenarian Study[1] recently identified nine factors related to being an autonomous 100-year-old (ie, having preserved activities of daily living, and good cognitive and social status)—good visual acuity; regular exercise; spontaneous awakening in the morning; preserved mastication; no history of drinking alcohol; no severe falls after age 95 years; frequent protein intake; living at home; and being male. Some opposite factors, especially a low level of exercise, a tendency to fall, and low protein intake, cluster in old-age frailty, and are composite factors that hinder successful ageing.

Instead of being an unavoidable consequence of accumulating years, frailty has been recognised as an independent geriatric syndrome.[2–5] The clinical characteristics are anorexia, sarcopenia, osteoporosis, fatigue, risk of falls, and poor physical health. Frailty can make elderly people highly vulnerable to adverse health outcomes, such as disability, dependency, need for long-term care, and death.[2–5] On the basis of US studies, frailty affects about 7% of people aged 65 years or older and about 25–40% of octogenarians or those who are older.

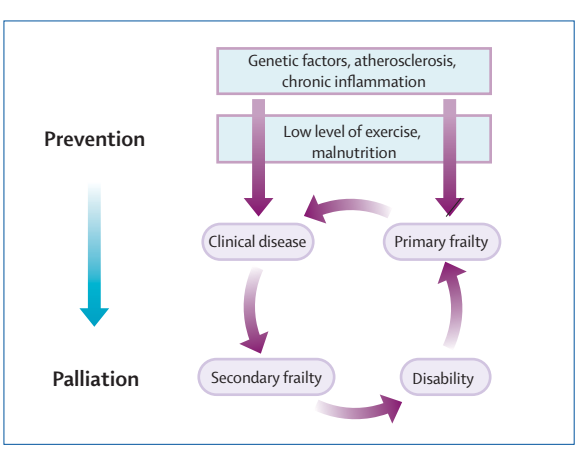

Figure: **Pathways to frailty**

Frailty arises from declines in the molecular, cellular, and physiological systems of the aged body. Frail elderly people have reduced stress tolerance because of decreased physiological reserves in the muscles, bones, circulation, and hormone and immune systems. The underlying mechanisms include genetic and acquired factors (eg, atherosclerosis and chronic inflammation).[5,6]

In a way that is analogous to dementia,[7] frailty might be a consequence of increasing entropy and gradual disorganisation of the body; however, at what stage does it become a pathological state? The presence of three or more of the five Fried criteria is increasingly used for clinical diagnosis: unintentional weight loss, exhaustion, low energy expenditure, slowness, and weakness.[4] The natural course of frailty is progressive, increasing the risk of comorbidity and disability over time. The term primary frailty can be used when the state is not associated directly with a specific disease, or when there is no substantial disability;[8] secondary frailty when the syndrome is associated with known comorbidity such as dementia or overt cardiovascular disease (figure).

Although most geriatricians intuitively recognise frailty, it is commonly neglected and confused with disability and various comorbidities. The increasing frequency of obesity in elderly people further complicates the clinical picture. For so-called fat-frail individuals,[5] frailty is actually inside and not readily apparent. The

substitution of muscle for fat is of particular concern, and combines the problems of frailty with those of being overweight.

Some physicians may even regard frailty as an example of the medicalisation of old age and be suspicious about its prevention. In its latest stage, frailty is similar to a terminal disease, the treatment of which must be symptomatic and palliative.[8] Two issues are important clinically: first, identification of the causes of frailty and its association with chronic inflammation and vascular disease; and second, establishment of the possibilities for prevention and their effectiveness.

Although prospective studies of the association between cardiovascular risk and frailty will take several decades to emerge, subclinical and clinical cardiovascular disease are probably important.[9] Frailty commonly coexists with coronary heart disease,[10] and is associated with an inflammatory state.[6,11] For effective prevention and treatment of frailty in elderly people, the syndrome (particularly the primary form) must be recognised and interventions need to start early. Therefore screening for frailty should be done in primary care.

Exercise to preserve and increase muscle mass and strength, and appropriate nutrition (especially adequate protein intake) are first-line treatments for primary frailty. Patients with secondary frailty also benefit from these interventions, alongside good care of the underlying disease and palliative care in late stages of frailty and disease. Furthermore, patients with frailty should be given appropriate treatment for pain and depression. Falls and their consequences should be prevented with multifactorial measures including balance control, vitamin D, hip protectors, and adequate treatment of osteoporosis. Immunisation against influenza, pneumococcal pneumonia, and herpes zoster can protect the frail body from acute and subacute strain.

Drugs for treatment of frailty are under investigation—eg, anabolic or anti-inflammatory agents, psychostimulants, and selective androgen-receptor modulators in elderly men.[12] However, treatment effects might be unexpected: megestrol improved appetite and promoted weight gain in frail elderly people, but decreased the benefits of strength training compared with those who did not receive megestrol.[13] Whether long-term use of common drugs for treatment of hypertension and heart failure (eg, those that prevent the effects of angiotensin II)[14] or dyslipidaemia (eg, statins with their anti-inflammatory and antiatherosclerotic effects) would help prevent frailty remains to be established.

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Clinical update: management of stroke

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Patients with suspected stroke (ie, "brain attack") require rapid assessment and intervention. Assessment aims to establish the diagnosis of stroke and its pathological and aetiological subtypes, and to forecast the prognosis for complications, recurrent stroke, survival, and handicap. Intervention aims to reverse any ongoing brain ischaemia or haemorrhage, to minimise the risk of complications and recurrent stroke, and to optimise physiological homoeostasis and rehabilitation.

The diagnosis of stroke remains clinical, despite research efforts to identify reliable biomarkers of brain infarction and haemorrhage. The clinical features that favour a diagnosis of stroke are: an exact time of onset; the presence of focal neurological symptoms, lateralising neurological signs, and abnormal cardiovascular findings (eg, atrial fibrillation, heart murmur); and being able to determine a clinical stroke subclassification.[1] Cognitive impairment and abnormal signs in other systems (eg, respiratory, abdominal) suggest a stroke mimic.[1] Diagnosis of stroke and transient ischaemic attack can be facilitated by diffusion-weighted MRI which identifies a relevant abnormality in most patients with recent ischaemic stroke (83%, 95% CI 78–88%) and in about half of patients with recent transient ischaemic attack (figure 1).[2] The diffusion-weighted MRI is more likely to be positive in patients with stroke who score more than 4 on the National Institutes of Health stroke scale and whose lesion is outside the brainstem, and in patients with transient ischaemic attack who have a history of a motor deficit, dysphasia, or dysarthria that lasted longer than 60 min (figure 1).[2]

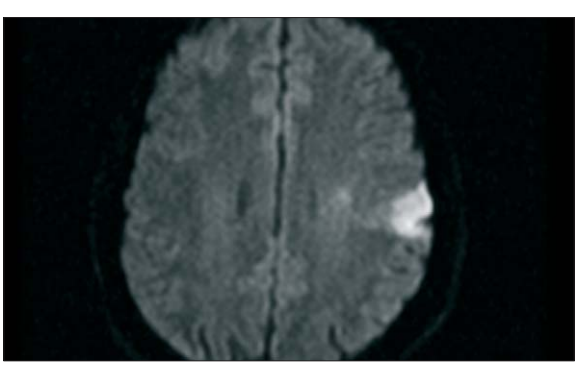

Figure 1: **Diffusion-weighted image MRI**
Figure shows area of restricted diffusion, consistent with ischaemia, in cortex and subcortex of posterior frontal lobe of left cerebral hemisphere in patient with transient ischaemic attack of brain that caused sudden onset of right arm weakness and difficulty speaking for 1 h. Brain CT scan was normal.

Haemorrhagic and ischaemic stroke are rapidly and reliably distinguished by plain CT brain scan.[2] The site of brain haemorrhage or infarction is a clue to the cause. MRI of the brain is more sensitive than CT for detecting the site and extent of focal brain ischaemia,[2] and for showing low-flow vascular malformations (cavernomas) and other vascular abnormalities. Proximal sources of thromboembolism in large arteries can be imaged non-invasively by ultrasound, MRI angiography, and CT angiography (figure 2). Transoesophageal echocardiography is better than transthoracic echocardiography for identifying sources of embolism in the aortic arch and heart; at least one in eight patients with normal transthoracic echocardiography have evidence on transoesophageal echocardiography of a potential source of embolism warranting anticoagulation.[3]

For patients with supratentorial non-aneurysmal intracerebral haemorrhage, early decompressive surgery is associated with a non-significant trend toward a reduction in death (odds ratio 0·85, 95% CI 0·71–1·02) but not dependency.[4] However, early surgery can reduce death and dependency in the subgroup of patients with lobar intracerebral haemorrhage (odds ratio 0·58, 0·36–0·92); a definitive trial in these patients is underway. Early haemostatic therapy with recombinant factor VIIa within 4 h of intracerebral haemorrhage retards growth of the haemorrhage but fails to improve patients' outcomes.[5]

For patients with ischaemic stroke, reperfusion within 3 h of onset with intravenous recombinant tissue plasminogen activator (alteplase), 0·9 mg/kg over 1 h, reduces death and dependency (odds ratio 0·64, 95% CI 0·5–0·8) despite an increase in brain haemorrhage.[6] Alteplase also seems to be safe and effective in routine clinical use.[7] Preliminary studies suggest that intravenous desmoteplase, 125 μg/kg 3–9 h after ischaemic stroke onset, is acceptably safe and can be effective for patients with MRI evidence of an ischaemic penumbra as defined by diffusion/perfusion mismatch.[6] Ongoing trials aim to resolve uncertainty about: the duration of the therapeutic time window; the optimum thrombolytic drug, route and dose; the independent baseline predictors of a response to thrombolysis; the role and timing of concomitant antithrombotic therapies; and the use of complementary therapies such as transcranial doppler

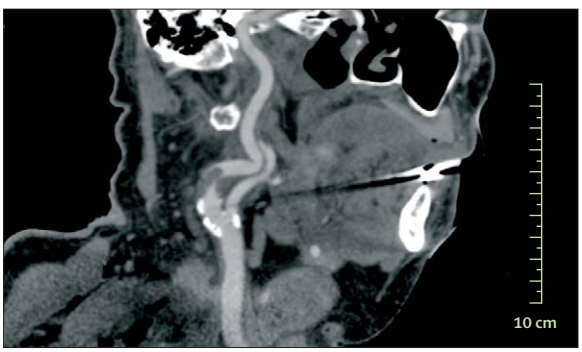

Figure 2: **CT angiogram**
Figure shows left common, internal, and external carotid arteries, with calcification (white) in terminal left common carotid artery, and calcification (white) and thrombus (black) causing very severe stenosis at origin of left internal carotid artery.

ultrasonography and mechanical clot penetration (with a microwire or microcatheter) and disruption (by balloon angioplasty, stent deployment, or snare device).[6] Early decompressive surgery within 48 h of onset of large, space-occupying, hemispheric ischaemic stroke reduces mortality and improves functional outcome in carefully selected patients.[8] Neurovascular protection with the free-radical scavenger NXY-059 was reported to improve functional outcome after ischaemic stroke, but a reanalysis of the data and subsequent larger trial[9] indicate this was a false positive. Ongoing trials continue to evaluate other strategies of neurovascular protection (eg, hypothermia) and treatments for complications of stroke (eg, graduated compression stockings for venous thromboembolism prophylaxis).[6]

After a transient ischaemic attack or minor ischaemic stroke, the overall risk of a recurrent stroke is about 5% within the first 2 days, 10% within the first week, and 18% within the first 3 months.[10] Risk factors for early recurrence are age 60 years or more, systolic blood pressure above 140 mm Hg or diastolic blood pressure above 90 mm Hg, clinical features of unilateral weakness or speech disturbance, duration of focal neurological symptoms over 60 min, and diabetes ($ABCD^2$).[10] Other possible adverse prognostic factors include recent symptomatic large artery atherosclerosis, multiple recent transient ischaemic attacks, embolic signals on transcranial doppler sonography, and a new clinically relevant lesion on CT or MRI brain scan.

For patients with ischaemic stroke or transient ischaemic attack due to atherothromboembolism, immediate and long-term aspirin reduces the relative risk of recurrent stroke and other serious vascular events by about 13% (95% CI 6–19%).[6] Oral anticoagulation is not more effective than aspirin because any possible protective effect against ischaemic events is offset by increased bleeding complications.[11] Long-term clopidogrel reduces the relative risk of serious vascular events by about 9% (0·3–16·5%) compared with aspirin.[6] Any benefits of clopidogrel combined with aspirin, compared with aspirin or clopidogrel alone, are offset in the long-term by cumulative risks of bleeding.[6,12] The combination of aspirin and extended-release dipyridamole is significantly more effective than aspirin (odds ratio 0·82, 0·74–0·91) and does not cause excessive bleeding.[13] Dipyridamole-induced headache can be reduced by starting with a low dose and gradual titration. A large trial comparing clopidogrel with the combination of aspirin and dipyridamole in more than 20 000 patients with recent (<120 days) atherothrombotic ischaemic stroke is expected to report in 2008.[14] Carotid endarterectomy is most effective for elderly men with a recent (within 2 weeks), non-disabling, carotid territory ischaemic stroke or transient ischaemic attack of the brain and an irregular or ulcerated symptomatic carotid plaque that is causing severe stenosis of the lumen.[15] Carotid angioplasty and/or stenting is associated with a non-significant trend toward a greater risk of perioperative stroke or death within 30 days compared with carotid endarterectomy (odds ratio 1·2, 0·9–1·6).[6,16,17] Whilst awaiting the results of long-term follow-up in ongoing trials comparing carotid stenting with endarterectomy, the use of carotid stenting (with an embolism-protection device) should probably be restricted to patients with recently symptomatic severe carotid stenosis and coexisting conditions that increase the risk of carotid endarterectomy, thereby precluding carotid endarterectomy.[6] Long-term reductions in systolic blood pressure by about 10 mm Hg and LDL-cholesterol by about 1 mmol/L are associated with significant reductions in risk of recurrent stroke and other serious vascular events by about 30% and 20%, respectively.[6,18] The effect of modifying other "newer" risk factors for stroke remains uncertain. Twelve trials to date show no evidence that B-vitamin supplementation (folic acid, vitamin B12, vitamin B6) significantly reduces the risk of serious vascular events, despite effectively lowering plasma homocysteine concentrations.[19] The results of ongoing trials of B vitamins in larger samples are awaited.

For patients with ischaemic stroke or transient ischaemic attack due to cardiogenic embolism, oral anticoagulation with warfarin (international normalised ratio 2·0–3·0) remains the most effective thromboprophylactic. The combination of clopidogrel plus aspirin is less effective than warfarin for prevention of serious vascular events in patients with atrial fibrillation, particularly those who are already taking warfarin (relative risk 1·44, 95% CI 1·2–1·8).[20] The direct thrombin inhibitor ximelagatran is not inferior to warfarin in efficacy but has an unacceptably high rate of adverse effects on liver function which has precluded its further development in atrial fibrillation. Warfarin is being compared with other direct thrombin inhibitors and with factor Xa inhibitors in ongoing trials.

For patients with aneurysmal subarachnoid haemorrhage in whom the aneurysm is considered suitable for both surgical clipping and endovascular coiling, the outcome is better with coiling.[6] Oral nimodipine (60 mg every 4 h) reduces the risk of delayed cerebral ischaemia and improves outcome.[6] Magnesium sulphate may also be effective in reducing the risk of delayed cerebral ischaemia (hazard ratio 0·66, 0·38–1·14) and a poor outcome at 3 months (risk ratio 0·77, 0·54–1·09). However, acetylsalicylic acid 100 mg suppositories, started within 4 days of aneurysm treatment and continued for 14 days, do not reduce delayed cerebral ischaemia (hazard ratio 1·83, 0·85–3·9).

Organised inpatient care and rehabilitation of stroke patients by a dedicated multidisciplinary team in a stroke unit reduces death and dependency.[6] Most deaths prevented would have occurred between 1 and 4 weeks after stroke due to recurrent cardiovascular events and the complications of immobility (eg, venous thromboembolism) and dysphagia (eg, aspiration pneumonia).[6] Stroke patients with mild to moderate disability who are discharged earlier than usual from hospital (by about 8 days) and continue their rehabilitation at home with a coordinated specialist multidisciplinary team have a lower risk of long-term dependency and admission to institutional care than similar patients who continue their rehabilitation in hospital.[6]

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Japan unveils 5-year plan to boost clinical research

This month the Japanese Government launches a two-pronged initiative to speed up drug approval and build a competitive environment for clinical trials in the country, which has traditionally been a strong base for basic research. Justin McCurry reports from Tokyo.

Seriously ill patients in Japan are being denied essential treatment because of delays in approving existing drugs and an exodus of home grown pharmaceutical firms that choose to undertake clinical trials overseas. That was the stark warning issued by health experts to coincide with the launch this month of a two-pronged Japanese government initiative to cut the "drug lag" and build a competitive environment for trials of new medicines in the world's second-biggest pharmaceuticals market.

Under the 5-year plan, the Health, Labour and Welfare Ministry will invest 1·75 billion yen (US$ 1=120 Japanese Yen) to develop 40 key facilities in an attempt to accelerate Japan's drug trial and approval processes. Ten bodies will work on securing the consent of trial candidates, while 30 core hospitals will undertake tests.

Testing times

The pressure for a quicker approval and testing process comes amid concern about rising health-care costs in a country with one of the oldest populations in the world, and where cancer and lifestyle-related diseases are expected to take their toll in the coming decades.

Health authorities say they are aware that costs will only be kept at manageable levels if Japan can take its vaunted scientific research to the trial stage and quickly channel existing drugs into the US$60 billion domestic market. To achieve that, drug regulators vowed to bring the time it takes to approve new medicines in line with the US and Europe by 2012. In addition, the Pharmaceuticals and Medical Devices Agency (PMDA)—Japan's version of the US Food and Drug Administration—says it will add 240 new drug reviewers to its current staff of 340 during the next 3 years. The current set up "not only keeps patients from accessing new and efficient drugs, but also prevents manufacturers from introducing their own new products into the Japanese market", said PMDA chief executive Akira Miyajima.

Few doubt that Japan's drug approval and clinical trial process is in need of an overhaul. Typically, a drug takes 4 years after it has received approval in the US and Europe to find its way onto the Japanese market. In 1996, clinical trials in Japan lasted an average of 61 months, but by 2004 the time had lengthened to 88 months, according to the Japan Pharmaceutical Manufacturers' Association. Not surprisingly then, that the number of trial notifications in Japan fell from 722 in 1996 to 329 in 2004.

Venture companies that elsewhere are responsible for developing ground breaking drugs have a negligible role in Japan, accounting for around 4% of the total. In the US, by contrast, 45% of patent applications emanated from start-ups in 2000, more than double the number in 1991. Japan has just 60 venture pharmaceutical firms, compared with 1300 in the US and 700 in the EU.

In 1993, Japan gave notification of 160 clinical trials, according to the health ministry, falling to just 43 in 2001. The figure has since recovered to 96 but is still well below that of other Organisation for Economic Cooperation and Development (OECD) countries. "Japan has to take the initiative to fill the gap between basic research, which it is very good at, and clinical trials", says Yasuhiro Suzuki, a senior health ministry official. "If you look at the figures it is clear that Japan has fallen behind."

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The slow-down has had a substantial effect on Japan's place in the global clinical trials market, with its share shrinking from 21% in 1994 to just 11% in 2003. Little over 7% of Japan's national budget goes on health-care-related research and development compared with more than 26% in the US, according to OECD figures for 2003.

Economic costs

Japan's focus on basic research is illustrated by its greater presence in major scientific journals than in leading medical journals. In 2002, Japan contributed to around 8% of papers in *Nature* but was responsible for less than 4% of contributions to *The Lancet*,

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Basic research has taken precedent over clinical research in Japan

Panos Pictures

Japan's life sciences R&D hopes to respond to the country's rapidly ageing population

according to Japan's National Institute of Science and Technology Policy.

But this publication disparity is nothing compared to the wider economic costs. The Pharmaceutical Research and Manufacturers of America (PhRMA) estimates that delays to drug approval, and the parlous state of clinical research, costs the Japanese economy almost 11 trillion yen a year in poor health, loss of working hours, treatment costs, and GDP losses incurred by an underperforming pharmaceuticals sector.

"The goal should be to push forward the simultaneous global development of drugs", says Ira Wolf, PhRMA's Japan representative. "But Japan is so much of an outliner on this. The clinical trials system is extremely expensive and onerous, and many of the people involved in it—from managers to monitors—are not adequately trained."

Japan's drug pricing system—reductions occur every 2 years to keep costs to the national health insurance scheme to a minimum—is another reason why pharmaceuticals venture overseas, where drug prices are rising, in their search for profits, Wolf says.

Elderly society

The country's demographics mean that demand for new drugs, particularly those for cancer and other diseases associated with ageing, is expected to soar.

According to the 2005 national census 20·1% of the Japanese population are aged 65 years or over. In 7 years' time one in four people will fall into that age bracket. Japan's life expectancy, at 79 years for men and 85 years for women, is the highest in the world; by 2030, Japanese women will live an average of 88·5 years, according to a World Trade Organisation estimate.

Rapid population decline provides the backdrop to this seemingly unstoppable trend. In 1947, Japanese women each gave birth to an average of 4·5 children. 60 years later, the fertility rate has plummeted to just 1·26 children, one of the lowest in the world.

The rapid ageing of Japanese society will lead to a rise in medical expenditure. Spending on health and welfare is expected to reach US$664 billion by 2010, compared with $496 billion in 2002, according to some estimates. Until now, only a tiny proportion of the total went on prescription drugs.

Per head medical spending on elderly Japanese is 4·9 times higher than for those aged under 59 years. This figure compares with 3·4 times in the UK and just 2·7 times in Germany, according to OECD data.

Drug lag

In view of the background demographics, the need for both new drugs and the speedy approval of existing ones is great. To its credit, the health ministry has targeted cancer drugs for early approval, but the fact remains that 39 of the 99 best-selling drugs around the world are still not available to Japanese patients.

Drugs that are already marketed overseas take an average of 4 years to be approved in Japan, compared with about 18 months in the US and Britain. "To the Japanese authorities that must be politically unacceptable", says Bruce D Forrest, executive director of Research and Development (R&D) in Japan for Wyeth, the US pharmaceuticals and health-care products firm.

A few encouraging signs have emerged amid the general despondency. Several Japanese pharmaceutical firms have recently committed large sums of money to research and development in the quest for new revenue sources as the patents on existing drugs expire. Earlier this year, for example, drug firm Eisai announced it would raise R&D spending by 10% to about 120 billion yen in fiscal year 2007 in an attempt to push through new drugs for breast and prostate cancer and Parkinson's disease.

For the most part, though, the immediate benefits will be felt far from Japan's shores. Eisai's potentially life-changing experimental drugs are all being tested overseas. The breast cancer drug, known for now as E7389, is in phase III trials in the US and Europe; the same is the case for the Parkinson's drug, E2007.

Overseas exodus

The hollowing out of the Japanese pharmaceutical industry has led to the cancellation of work on candidate compounds for a range of ailments. It is a familiar paradox—the cancellation or flight overseas of promising treatments pioneered in Japanese university laboratories.

Japanese scientists are responsible for some of the most effective drugs of recent times. They include azidothymidine (AZT), an antiretroviral, and atorvastatin (Lipitor)—the biggest-selling drug in the world.

Several firms, including Wyeth and AstraZeneca, have committed themselves to drug trials in Japan this year, but they remain in the minority.

The prohibitive costs and dearth of financial incentives at home force Japanese pharmaceutical firms to undertake clinical trials overseas, thereby extending the wait for patients back home.

Eisai, for example, sells more than half of its products outside of Japan, with Fujisawa and Takeda not far behind. In 2000, Japanese companies tested 70 drug entities beyond its own shores and only 33 at home. Few new drugs that are available in Japan actually originate there: in 2005, almost three-quarters of new drugs on the domestic market came from overseas.

There are some encouraging signs, with Japan-based arms of major pharmaceutical firms now involved in clinical trials for several Alzheimer's drugs, but again there is a substantial lag. Japan has only one type of medication for Alzheimer's and has yet to approve rivastigmine, which is already on sale in more than 70 other countries.

Playing catch-up

Health officials argue that Japan has been forced to play catch-up by a change in the patent laws that took place in 1975, which ended the practice of synthesising the chemical compounds of existing drugs and selling them as new products.

"Until 1975 there was no essential need for clinical research in Japan", says Tatsuo Kurokawa, a councillor in the pharmaceuticals and food safety division of the health ministry. "At the same time there was little need for professionals who were capable of carrying out that research. We are playing catch-up because we have only 30 years of experience in the field."

Officials concede that persuading doctors to become involved in clinical trials will be an uphill struggle. The financial incentives that woo doctors in Europe and the US are non-existent in Japan, where drug trials are not rewarded with extra cash but, if they take place at all, regarded as a part of a doctor's regular duties. Not surprisingly then, critics say, that clinical research is so far down the list of a busy physician's priorities.

"Basic studies involving animals and organs produce clear data and don't take much time, but clinical trials are time-consuming and there are considerable risks involved in getting a satisfactory result", Kurokawa concedes. "They may find that all their effort has gone to waste."

Mark Colby, a lecturer at Chiba University and author of *Negotiating the Gray Maze: The Business of Medicine in Japan*, welcomed the health ministry initiative as a sign that the discussion on clinical trials is "out of the closet," but said the lack of a trial infrastructure was a key obstacle to progress.

"Doctors simply don't want to take part in clinical trials—they're busy, and there's absolutely no financial incentive", he said. "The hassle involved in complying with Japan's patient privacy laws makes it difficult for doctors to go in and get permission. Then they have to convince patients, who are told that the drug is experimental and, in any case, they might end up being given the placebo."

Risk averse

Patients are not the only group that needs convincing of the potential

Panel: Drug lag for depression

Few areas highlight the adverse effect of Japan's slow approval process for drugs available overseas than the treatment of psychological illnesses. The Pharmaceutical Research and Manufacturers of America (PhRMA) claims that up to 1 million Japanese people a year do not have access to treatment for depression simply because of where they live.

For decades, social taboos prevented people with psychiatric problems from seeking help. Few were willing to discuss their problems outside of the family, if at all, and even fewer considered clinical intervention an option. Health officials, however, have started to recognise the need for action, partly because of the pronouced warning signs about the state of the nation's mental health offered by yearly suicide statistics.

An estimated 30 000 Japanese people kill themselves every year, one of the highest per head rates in the world. Figures show that 25 people in every 100 000 kill themselves, more than twice the rate in the US. Furthermore, only 15% of Japanese with diagnosable symptoms of depression receive treatment.

The introduction of paroxetine (Paxil) is thought to have helped cut the suicide rate substantially in the US in the 10 years after its introduction there in the late 1980s. Patients in Japan, however, had to wait 11 years for the drug.

Even after the drug was available in Japan, many doctors were reluctant to use it. "Why is that happening?", asks Ira Wolf, PhRMA's Japan representative. "It certainly raises questions about the direct impact the drug lag is having on people's lives". The result is that Japanese patients are being treated with drugs with severe side-effects that are increasingly seen as a last resort in many other countries.

"A significant problem in Japan is that they are still playing catch-up with drugs that were available 10 years ago—particularly those for depression—because of a belief that the Japanese had different symptoms and disease complex", says Bruce D Forrest, executive director of R&D in Japan for Wyeth, the US pharmaceuticals and health-care products firm.

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Scandals involving medical products have created a risk-adverse environment

benefits of controlled risk-taking. Recent scandals involving medical products have had a sobering effect on health officials, and created an environment that some say is too risk averse.

The infection with HIV of as many as 2000 Japanese haemophiliacs in the 1980s, when health authorities approved the use of unheated blood products despite warnings they could be contaminated, continues to cast a shadow.

The recent ban on prescriptions to teenagers of the influenza drug oseltamivir (Tamiflu)—amid reports of abnormal neuropsychiatric reactions—risks creating even more cultural reticence towards new treatments. "Japanese firms are not by their nature risk takers", the health ministry's Suzuki said.

International collaboration

One possible way to boost clinical research lies with a landmark agreement reached almost a decade ago. Japan's decision in 1998 to sign up for an agreement with the US and Europe to permit the use of data acquired overseas—keeping the amount of domestic data required to a minimum—has given it the means to become more engaged in clinical trials.

The International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) permits regulators in one country to use safety and efficacy data already submitted in another.

Last month, the private sector called on Japanese health authorities to give priority to screenings of candidate drugs that can best be tested in international cooperative trials. Japan is also looking at regional trials for drugs that promise to tackle conditions that are problematic in east Asia.

"It is essential to set out the best clinical trial methods for specific drugs, such as global trials for products that face severe competition and [for] companies [that] want to get ahead of everyone else, as well as region-specific trials for medications targeting stomach cancer and hepatitis commonly found in Asia", said Masaru Iwasaki, an authority on international clinical trials.

In a sign of what could be achieved, Banyu, the Japanese affiliate of the US firm Merck and Co, recently rolled out losartan potassium (Nu-Lotan), which is used to treat conditions associated with diabetes. According to local media reports, this was the first time Japan had approved a drug that had been tested simultaneously at several institutions around the world.

Yet approval in Japan took 4 years—twice as long as usual—compared with little over a year in the US, mainly because of local resistance to the use of data from non-Japanese trialists.

The 1998 agreement should have signalled a breakthrough, but Japanese foot-dragging has tempered the effects of harmonisation. One stumbling block is concern about the efficacy of data that does not take into account the possibility that Asians react differently to certain drugs than other ethnic groups. And finding Japanese trialists is next to impossible, health experts say, particularly when large numbers are required for a new chemical compound.

The ICH tried to quell those fears with its Ethnic Factors Guideline, which states that "ethnically insensitive" drugs require no further testing, whereas others will have to be exposed to bridging studies to ensure that data on dosage, safety, and effectiveness apply in the target market.

Even so, Japan appears to regard itself as a special case. "There is no textbook style for the clinical development of new drugs", says the health ministry's Kurokawa. "There is always something different to consider. The only constant is safety."

Mild optimism

Outside policymaking circles, the government's latest plan to boost clinical trials has been greeted with mild optimism and open disdain.

Observers point out that the government will find it difficult to create proper testing sites as long as there is a shortage of trial nurses and clinical research coordinators in a country where clinical trial work is still regarded as a bad career option.

"The increase in regulatory staff is an important development, but they're only just starting to recruit those extra personnel, who will require a lot of training and experience, so the impact won't be felt for at least another 5 years", the PhRMA's Wolf says.

"I fear the money being thrown at core hospitals will just disappear", said Forrest of Wyeth pharmaceuticals in Japan. "It needs to go directly into training." Only when the environment is right, with trustworthy data available at the click of a computer mouse, will the industry feel moved to invest, believes Forrest.

"All stakeholders have to be on board for this to work. The government's response is to throw money at institutions but I'm not sure that is the answer. They can improve sites when the industry works with them. But not if Japanese firms continue to go overseas first."

Justin McCurry

Book

A singular theory of gender and the origins of dissection

A Martian writing the history of terrestrial medicine 500 years from now could be forgiven for recording that "it was not unknown for a female earthling undergoing hysterectomy in the late 20th century to make a gift of her womb to a male friend". After all, it is a documented fact that when film producer Raffaella De Laurentiis underwent hysterectomy she had her uterus bottled and sent to director David Lynch who keeps it to this day. If the Martian researcher were so minded, she could proceed from the observation of her single instance to the erection of a comprehensive theory which will reveal her own presuppositions far more effectively than it will illuminate the past.

In 1990 when Katharine Park began the researches that culminated with the publication of *Secrets of Women: Gender, Generation, and the Origins of Human Dissection*, she "planned to study the roots of human dissection in medieval Christian devotional and funerary practice", the supposition having apparently been made and accepted that human dissection did indeed have roots in Christian devotional and funerary practice. In *Secrets of Women* she seeks to parlay clusters of odd instances of female dissection into a general tendency or "ubiquity", although every reader of *Gray's Anatomy* knows that the paradigmatic human anatomy is male and the female anatomy consists of reproductive organs and nothing else. Though we might these days study the structures in the female human brain, it has not yet become the standard human brain.

The earliest case to be discussed in *Secrets of Women* is that of a Franciscan abbess, Chiara da Montefalco, whose body was searched in 1308 by her nuns post mortem for prodigious signs that would promote an already burgeoning cultus and bring her convent fame and fortune; two similar cases are cited, and the point made that no similar case can be found in the period in which the body to be searched is male. This in turn is interpreted as evidence that practice, already extremely rare, was "restricted to female bodies". There was no authority presiding over these events; in all three cases the procedures were informal, carried out by nuns of the community. What the nuns found inside the saintly Mother Chiara were three small gallstones and an impression of the crucified Christ imprinted on her heart. The consulting physician assured them that these could not have been naturally occurring structures. The church authorities, to their credit, retained a healthy scepticism for more than three centuries. Chiara was not canonised until 1881.

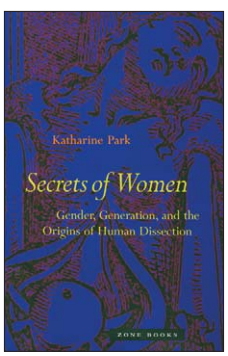
"When the systematic study of human anatomy gathers pace in the 16th century, men's bodies begin to be examined as dynamic structures. Nobody studied musculature in a female model; there are no écorchées."

Park goes on to argue "that knowledge of the body's interior based on anatomy and dissection was represented in late 13th- and early 14th-century Italian learned discourse as male and public, in opposition to characteristically female and secret forms of knowing, and, second, that the female body emerged during the course of this period as the ideal type of body, with a secret and hidden interior, the paradigmatic object of dissection". Even the female body is not constructed around a void; it is precisely the vulgar notion of the female body as a passive container that limits investigation of the female anatomy to the organs of generation. Not for nothing were the parts of the matrix given the same names as the parts of the brain; the uterus was, as it were, the female brain. When the systematic study of human anatomy gathers pace in the 16th century, men's bodies begin to be examined as dynamic structures. Nobody studied musculature in a female model; there are no écorchées. The female body was not skinned but opened, like a box; indeed female models in which the abdomen could be opened, the uterus exposed and opened in its turn and a model of the fetus taken out were highly prized objets de vertu.

Park moves rather swiftly to late 15th-century Florence and the autopsy carried out on the body of Fiametta Strozzi at the request of her husband. Fiametta seems to have died 3 weeks after her seventh confinement as a consequence of a retained placenta. Such privately ordered autopsies were becoming commoner at the turn of the 16th century but they were never common. At this point, Park's argument becomes difficult to follow:

> "The relative lack of occupational organisation and autonomy on the part of Italian midwives may reflect the early involvement of Italian physicians in treating women in matters relating to generation and birth. This did not represent a 'usurpation' of the functions of midwives by physicians…"

Obviously. A physician trained at Padua or Bologna was not expected to touch the body of the patient. What was expected of him was a learned opinion, a diagnosis possibly, and a prescription certainly. Wounds of all kinds, burns, fractures, gashes, were daily occurrences and none of them was dealt with by a physician. Bone-setting and suturing were learned by surgeons and women as manual skills, by watching and copying. The women and barber-surgeons who carried out



Secrets of Women: Gender, Generation, and the Origins of Human Dissection
Katherine Park. MIT Press, 2006. Pp 304. US$36·95, £23·95. ISBN 1-890951-67-6.

everyday procedures understood and recognised the structures they were dealing with, but they could not name the parts. The great change happens when the son of a surgeon, Berengario di Carpi, acquires a humanist education and sets out the practical knowledge he acquired as his father's assistant in an illustrated Latin text.

The father who summoned a physician to his wife's confinement was displaying both a fitting concern for his progeny, if not for his wife, and his spending power. It was the midwife's duty to attend the woman from the onset of labour to the outcome; the physician came and went, much as the consultant obstetrician does now. Park muddles the situation:

> "Rather it seems that male physicians began to provide more medical services to women in matters in which these women had received little or no specialized care of any sort and had relied instead on the advice of female family, friends, and the occasional empirical practitioner."

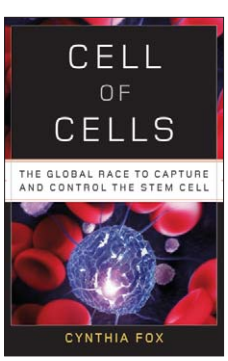
The only medical service a physician provided in 16th-century Italy was words, very expensive words, that became even more expensive when they were translated into the apothecary's receipts, in which the costliness of the ingredients had far more to do with the patient's ability to pay than with any therapeutic function. The organisation and licensing of midwives was sometimes undertaken by the ecclesiastical authorities, but it was more often a matter of local knowledge. We know from surviving letters that families sought out the most respected midwives and booked their services in advance. The popular impression was that the woman whose labour was complicated by the presence of a physician would be lucky to survive.

Most of what passed for medicine before the 17th century was self-important, self-protective humbug. Park's second last case, of Elena Duglioli, involves a self-professed virgin who lactated. As she lay dead in the Church of San Giovanni in Monte in Bologna in 1520, milk was expressed from her breasts.

> "...her most devoted supporters suckled from Elena's corpse, which was then eviscerated and embalmed by two local surgeons."

The faithful, scenting a miracle, were already congregating. Unfortunately the local surgeons threw away the uterus with the other gizzards, so the most likely cause of Elena's lactation was never eliminated. No reliable hypothesis can be erected on evidence so singular. It is a positive relief to emerge from such hocus-pocus into the luminosity and proportion of Vesalius and Berengario, but sobering to reflect that the poor understanding of the functions of the normal female reproductive system, in particular menstruation, that Park castigates in them, persists in our own time. The well woman is almost as mysterious a creature today as she was in 1500.

Germaine Greer
c/o *The Lancet*, London, UK



Cell of Cells: the Global Race to Capture and Control the Stem Cell
Cynthia Fox. W W Norton & Company, 2007. Pp 512. $26·95.
ISBN 0-393-05877-2.

In brief

Book The stem cell race

Peopled with quirky characters and crowded with strange and beautiful places, *Cell of Cells* reads like the best travel writing, but the author doesn't stint on the science, or the politics, of her subject. Cynthia Fox spent years touring the world's stem cell hotspots, staking out labs from Egypt to Israel to Singapore, and peering over the shoulders of scientists and surgeons. Her exhaustive legwork has produced a highly entertaining book.

Dozens of key stem cell scientists get personality profiles, as well as a thorough accounting of their work and thought, including Israel's Shimon Slavin, the bone marrow transplantation pioneer who is now using stem cells to create dual immune systems; Jerry Yang of the University of Connecticut's Center for Regenerative Biology, the first scientist to clone an adult farm animal; and Harvard's Jonathan Tilly, who overturned decades of medical dogma by demonstrating the existence of mammalian oocyte stem cells. We get to know patients treated with stem cells, and are offered a surgeon's-eye view of their operations.

Fox's often wry tone is ideal for capturing the excitement, and the hype, that accompany any promising medical advance. Fascinatingly, she was researching the book during the spectacular fall of Seoul National University researcher Hwang Woo Suk, whose reports of making the world's first human cloned stem cells were eventually exposed as fraud. We follow Hwang on his way up, basking in the attention of admirers at international meetings and whisking Fox through his state-of-the art lab. And when the time comes to tell of Hwang's disgrace, Fox does an excellent job of helping the reader keep the characters involved, and their misdeeds, straight.

Cell of Cells opens with the words of researcher Susan Fisher: "Science is like a stream of water. It finds a way." And Fox provides us with a compelling account of just what this means in today's world of "presidential lines", Singaporean billions, and scientists as rock stars. Let's hope she brings us along on her next voyage.

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Profile

Tatsuo Kurokawa: keeping watch on drug safety in Japan

Not surprisingly for a career bureaucrat, Tatsuo Kurokawa would rather not be the centre of attention. But as the Japanese government's point man on drug safety, he now finds himself at the centre of a storm over claims that oseltamivir (Tamiflu), the widely used influenza drug, is behind the deaths of a few young patients and responsible for cases of abnormal psychiatric behaviour. As he sits down to talk at his office in the labyrinthine premises of Japan's Ministry of Health, Labour and Welfare, he is guarded about Japan's response to the furore over the oseltamivir, and seems more comfortable discussing his country's much-maligned record on approving drugs for the domestic market. His job, he says, "is not to promote clinical trials or the approval of new drugs, but to evaluate applications and weigh up the benefits and risks to patients".

Critics say that Japan's "drug-lag" is the result of bureaucratic foot-dragging and a poor review and approval infrastructure that has produced the stark statistic that 39 of the world's top-selling drugs are not available to Japanese patients. The drugs that do emerge are sometimes launched in Japan years after they went on the market in the USA and Europe. "For the Japanese government that must be politically unacceptable", says Bruce D Forrest, executive director of R&D in Japan for Wyeth, the US pharmaceuticals and health-care products firm. Kurokawa's response is uncharacteristically frank: "That is what [international observers] say, but it's not our position. The real issue is to what extent our supply meets the needs of patients and physicians in Japan who are battling diseases and symptoms. In many cases there are already similar types of drugs available in Japan." He said the ministry had worked hard to speed up the process for testing new drugs and approving existing ones to treat cancer, for example, but that those efforts had gone largely unnoticed outside Japan.

Kurokawa accepts, however, that Japan is still playing catch-up in the area of clinical trials. He traces the cause of that clinical research atrophy to a 1975 legal change under which patents were applied to the chemical compounds of medicines developed overseas, thereby preventing Japanese firms from reformulating the drugs and selling them as "new" products. "Until 1975 there was no essential need for clinical research in Japan", he says. "At the same time there was little need for professionals who were capable of carrying out that research. We are playing catch-up because we have only 30 years of experience in the field." Although he claims that the process has "picked up considerably", Kurokawa acknowledges that many Japanese doctors seem to find work in clinical trials an unattractive prospect.

But tackling the drug-lag will have to wait while he and his ministerial colleagues attempt to resolve the crisis about oseltamivir. Last month Japanese health officials told doctors not to prescribe the drug to patients aged 10–20 years amid reports that some adolescents had shown bizarre behaviour after taking the drug, with a few unusual suicides. The decision drew an immediate rebuke from oseltamivir's manufacturers Hoffmann-La Roche. And so it was the Kurokawa found himself stuck between a pharmaceutical giant and the families of the victims, some of whom accused his department of waiting too long before taking action. That charge gathered weight when the oseltamivir panel, on which Kurokawa sits, revealed that psychiatric problems had been reported in 128 patients in Japan since oseltamivir went on sale here in early 2001. Now he admits that "the dust is still settling, but for the moment safety is the most important consideration of all". He now faces a difficult few months as he and other clinical experts sift through each case in an attempt to establish, or dismiss, a causal link with oseltamivir. The results, he says, will be made public "as soon as possible". It is fair to say that he will need to summon all of the diplomatic skills he acquired working at WHO headquarters in Geneva and at its Western Pacific Regional Office in Manila from 1980–82.

A graduate in pharmaceutical sciences from Japan's Chiba University, Kurokawa joined the university's new drug division in 1989 and coordinated Japan's participation in the international conference on harmonisation of pharmaceuticals. In the mid-1990s, he headed the Japanese government's Office for the Promotion of the Appropriate Use of Drugs and completed his doctorate, an international comparison of new drug development and evaluation. He took up his current post as councillor for pharmaceuticals and drug safety in the health minister's secretariat in 2004.

Besides depriving him of sleep, the oseltamivir issue has, he says, reminded him that his ultimate responsibility is to the consumer. He is also clear that "If there are promising new drugs available, of course, speed is of the essence and we as regulators don't want to impede them unnecessarily. We want people to enjoy the harvest of medical progress, but without ever compromising safety. We are talking about drugs, remember, not types of tea or bread." One senses that Kurokawa almost relishes resuming his mission to end the stagnation that blights Japan's approval regime for new drugs: "We are facing a very difficult future in which we will have to tackle cancer and other very serious diseases, particularly those associated with ageing. So yes, we are going to need new, improved, and safe drugs. And I won't rest until we have them."

Justin McCurry
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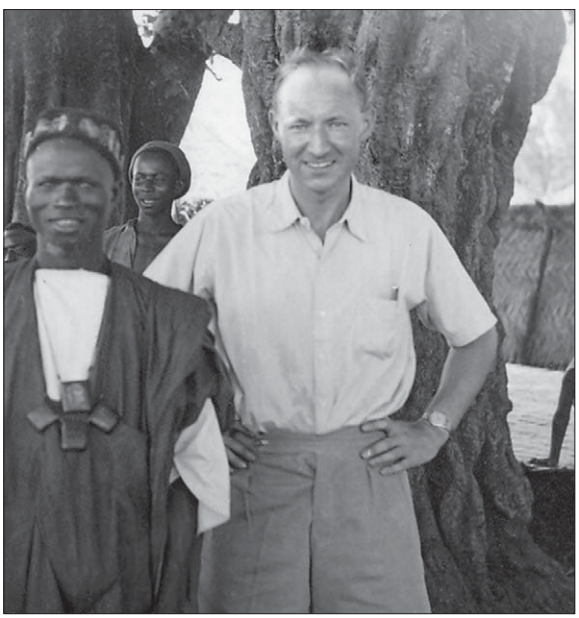
See **Special Report** page 1333

For more on **oseltamivir** see **Editorial** *Lancet* 2007; **369:** 1056



Sir Ian Alexander McGregor

Malariologist who led research for the UK's Medical Research Council in The Gambia. He was born on Aug 26, 1922, in Cambuslang, Lanarkshire, UK, and died on Feb 1, 2007, in Salisbury, Wiltshire, UK, aged 84 years.

When Herbert Gilles, now emeritus professor at the UK's Liverpool School of Tropical Medicine, first went to The Gambia to work for Ian McGregor, in 1954, the research facilities in the remote province of West Kiang, where McGregor's unit was based, were rudimentary. "We had the microscope of course, but the 'lab' was just a table and a microscope in a room that also served as the dining room and the sitting room", Gilles recalls. By 1967, however, when another scientist, Iain Wilson, who now runs a parasitology research group at the UK's National Institute for Medical Research, came to join the team, McGregor had established an impressive research unit. "They even had centrifuges. I was surprised by how good the lab was", Wilson says.

At the time Wilson started working for McGregor, the Gambian unit that McGregor led—an outpost of the UK's Medical Research Council (MRC) in Fajara—was already developing a reputation for excellence in malaria research, after starting out in 1948 as a Field Research Station focused on nutrition. McGregor was drafted in a year after the centre's launch to set up a long-term project in three villages—Keneba, Manduar, and Jali—to assess the effects of treatment of various diseases on health and nutrition.

After taking over as the centre's director in 1954, and working closely with his wife, Joan, McGregor set up a census of local villages and used this work as a starting point for a long-term study. According to Wilson, McGregor had a rapport with indigenous communities that had enabled him to gather blood samples from people infected with malaria, including children. "When we were up country and some of the villagers were not too keen to have blood samples taken, Ian would stand back a little and joke with them and eventually they were happy to be involved. This was important in terms of getting the full records of people whenever he visited the villages", Wilson recalls. The resulting demographic database for the village community of Keneba is now famous in tropical medicine, according to Wilson. "There are not many people who come to the same village areas year after year and examine people and get birth and death certificates", says Gilles. "This a very unique situation."

McGregor first developed his interest in malaria after being posted to Egypt during World War II, soon after completing his medical education at St Mungo's College, Glasgow. He was subsequently sent to Palestine, where he was responsible for malaria control throughout Israel and Transjordan. On his return from the Middle East, McGregor worked at the London School of Hygiene and Tropical Medicine, London, where he met Professor B S Platt, then Director of the MRC Gambian research unit, and was invited to move to Africa, where he stayed until 1980, at which point he returned to the UK and took up a visiting professorship at the Liverpool School of Tropical Medicine.

Alongside his commitment to epidemiology and community health, McGregor was interested in the mechanisms of acquired immunity to malaria. In collaboration with Sidney Cohen, he showed that infusions of serum from adults deemed clinically immune from malaria could protect children from the disease. Brian Greenwood, a professor at the London School of Hygiene and Tropical Medicine, says McGregor's work provided the first indication that it would be possible to develop a malaria vaccine: "Before this study was done, it was known that after repeated exposure to malaria, adults developed some protection against severe forms of the infection but this study showed for the first time that this was mediated, at least in part, by something present in serum, almost certainly antibodies." According to Greenwood, McGregor's greatest contribution was showing the value of painstaking longitudinal studies to tease out the contributions of factors, including climate, nutrition, and infection, to overall health. He believes that McGregor's work in "establishing a site at Keneba where this kind of study could be done was highly innovative and has provided a rich reward in many areas of health that affect African children. This would not have been possible without his foresight." McGregor is survived by his wife, Joan, and his children, Lesley and Alastair.

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Postgraduate Medical Education and Training Board (PMETB)

In their Comment on selection for specialist training (March 24, p 967),[1] Morris Brown and colleagues refer to "grave short-comings" of the UK's Postgraduate Medical Education and Training Board (PMETB) but omit to say what these are. They correctly also refer to confusion over who does what in postgraduate medical education.

PMETB was established after recommendations going back at least to the Merrison Committee of the 1970s,[2] but particularly in the wake of the Bristol Royal Infirmary Inquiry,[3] which concluded that postgraduate medical education should be regulated, just as undergraduate had been—very successfully—for nearly 150 years.

PMETB is quite separate from the Modernising Medical Careers (MMC) initiative. PMETB creates standards, MMC creates structures. PMETB is an independent, UK-wide body with statutory powers over the content and standards of postgraduate medical education. Our responsibilities include approving specialist training curricula and assessments, but these are devised and submitted to us by the medical profession, through the medical Royal Colleges, often acting in conjunction with the specialist associations. The curricula are not dependent on a particular type of training structure, but the knowledge, skills, and attitudes that they require must be demonstrated by appropriate assessments before a certificate confirming completion of training can be issued.

Since we began operation in September, 2005, we have achieved much: in addition to reviewing and approving all curricula to ensure consistency across specialties, we have introduced the first ever generic standards for training, undertaken the first ever survey of UK trainee doctors, developed and implemented new routes to the specialist and general practitioner (GP) registers, and certified more than 5000 doctors, enabling them to take up GP and consultant posts in the UK.

PMETB is not responsible for the operational aspects of selection, or for workforce issues such as the number of training posts. We do, however, set the overarching standards within which selection must operate. We reviewed the framework for delivery of the Medical Training Application Service (MTAS) against these principles in August, 2006, and noted some concerns, but were assured that these were being addressed. Our letter to MTAS has been in the public domain for some time.[4] We undertook to review the operation of the new system once it had been established. This review will take place, looking forward to 2008 and drawing on the learning of 2007.

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MRI versus CT in acute stroke

Julio Chalela and colleagues (Jan 27, p 293)[1] compare the accuracy of MRI and CT for the diagnosis "acute stroke". Although they included patients up to 8 days after stroke onset, they called it "emergency assessment". Patients with transient deficits (number not given), but with "imaging evidence of cerebral infarction" (not defined) were diagnosed as having "ischaemic strokes". This is circular reasoning and a self-fulfilling prophecy: not surprisingly, MRI has the best accuracy for an MRI-defined stroke.

The feasibility of doing stroke MRI was higher than in other studies,[2,3] presumably because many patients had minor strokes. Under these conditions, Chalela and colleagues found that MRI is more sensitive and as specific in detecting ischaemic stroke than CT and as sensitive and specific in detecting acute brain haemorrhage. They did not show, however, that MRI findings have a therapeutic effect and can improve clinical outcomes. Nevertheless, Chalela and colleagues state that MRI "might increase the cost-effectiveness of stroke care" and quality of stroke outcomes, and conclude that MRI "should be the preferred test for accurate diagnosis of patients with suspected acute stroke".

This is unfortunate, because such speculation might dissuade physicians in less wealthy institutions from treating patients on the basis of CT findings only. Chalela and colleagues do not mention that the treatment of acute ischaemic stroke on the basis of minimal image information—ie, the exclusion of brain haemorrhage with CT—is highly effective.[4] Whether early reperfusion strategies might be beneficial even without any image information has not been studied yet.

We declare that we have no conflict of interest.

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Authors' reply

The primary objective of our investigation was to compare the diagnostic information contained in non-contrast CT with that of non-contrast MRI in the full range of patients with stroke-like symptoms presenting to a community hospital. We believe that this situation reflects stroke care provided outside of tertiary care centres since the initial assessment and decision to use imaging was initiated by the emergency physician. The superiority of MRI was driven by a fivefold greater detection of radiological signs of acute ischaemic stroke and a greater degree of diagnostic agreement among expert readers.

Rüdiger von Kummer and Imanuel Dzialowski's concern about our inclusion of patients 8 days from onset neglects several relevant facts: the median time from onset to scan was about 6 h (IQR 3–9); the results were the same when the time from onset to scan was within 12 or 3 h; and limiting the range of patients selected would have made the results less generalisable.

To assuage their concern about our definition of infarct versus transient ischaemic attack, we repeated the analysis in all patients with a clinical diagnosis of definite or probable acute ischaemic cerebrovascular syndrome,[1] whether or not the deficits were transient or the scan was read as positive by the treating stroke physician. This analysis confirmed the extent of MRI's superiority in accuracy and sensitivity.

Lastly, von Kummer and Dzialowski are concerned that MRI use has not been shown to improve patients' outcomes. Because patients diagnosed with acute ischaemic stroke are offered interventions of proven clinical benefit (eg, thrombolysis, inpatient stroke units, secondary prevention medicines), greater diagnostic accuracy must of logical necessity lead to better outcomes in stroke patients correctly diagnosed than in their misdiagnosed counterparts. Future studies might quantify the size of that effect.

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Julio Chalela and colleagues[1] stress that MRI is the current gold standard in imaging acute stroke. Indeed, MRI is an invaluable tool with which to visualise, within minutes of cerebral infarction, what is believed to be the core (area that is already dead) and the penumbra (tissue at risk that might either die or survive).[2] By contrast, conventional CT has only limited use in detecting acute ischaemic stroke.[3] However, the emergency assessment of most stroke patients still relies on CT alone.

In recent years, perfusion CT and CT angiography have been introduced in imaging acute stroke. Since then, surrogate markers of perfusion CT that correspond to core and penumbra have been defined.[4] There is a good correlation between the core and penumbra as assessed by perfusion CT and MRI.[5] One drawback of perfusion CT is the restriction of the anatomical coverage of most multidetector scanners compared with MRI. However, the development of more powerful multidetector CT machines might overcome this limitation. Finally, CT angiography allows the visualisation of the neck and brain arteries with a high resolution.

In summary, perfusion CT combined with CT angiography is an inexpensive and promising alternative in the emergency assessment of stroke patients where access to MRI is unavailable or restricted. Moreover, the advances in CT might soon allow us to guide our decisionmaking regarding thrombolytic treatments in the emergency setting beyond the current 3-h time frame.

We declare that we have no conflict of interest.

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The paper by Julio Chalela and colleagues on MRI in acute stroke[1] was assessed in a critical appraisal exercise by 13 participants in an advanced education programme on cerebrovascular diseases, organised by the University "La Sapienza" in Rome, Italy.

In a pre-evaluation survey, participants were asked whether, in their opinion, MRI should replace CT for the diagnosis of acute stroke. Answers were almost balanced between "yes" (seven) and "no" (six). Further discussion led the panel to conclude that MRI is: (a) a valid test for acute stroke; (b) more sensitive and specific than CT to diagnose brain ischaemia; (c) as helpful as CT in

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identifying haemorrhagic stroke; and (d) its use in the emergency setting should be assessed on the basis of pretest probability. The latter deserves a few additional remarks.

The proportion of patients with a definite stroke seen by Chalela and colleagues (61%) is much lower than that reported from comparable settings,[2,3] where emergency department physicians correctly identified 89–91% of acute stroke patients before doing brain imaging. A high pretest probability is likely to offset the expected advantage of MRI over CT.[4] Moreover, CT is as helpful as MRI in identifying bleeding, which cannot be clinically detected. Therefore, when a patient's referral for brain imaging is based on a good-quality clinical examination, MRI is no better than a standard CT scan.

In our post-evaluation survey, all participants agreed that MRI should replace CT if a low pretest probability of acute stroke (eg, 60–70%) is expected.

Students who assessed the paper were: Flavia Angelucci, Sabrina Anticoli, Flavio Arciprete, Rita Bella, Marcella Caggiula, Roberto Frediani, Rosathea Giugliano, Antongiulio Guadagno, Domenica Le Pera, Alessandra Martignoni, Giordana Pelone, Francesca R Pezzella, Sebastiano Uselli.

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Meningococcal vaccine coverage in Hajj pilgrims

As one us (ZAM) wrote with Qanta A Ahmed and Yaseen M Arabi,[1] Saudi residents undertaking the Hajj pilgrimage must be immunised, and non-immunised local inhabitants of Mecca are offered the vaccine free of charge, whether or not they undertake the pilgrimage. After the 2000 and 2001 outbreaks of Hajj-associated meningococcal infections, meningococcal quadrivalent polysaccharide vaccine became a mandatory requirement for pilgrims.[2] Despite this rule, coverage is still too low in local pilgrims.

During the 2006 Hajj, we surveyed 134 male British and 109 male Saudi pilgrims (including resident non-Saudis) who attended Mecca's British Hajj Delegation and the National Guard Clinics, respectively, to compare meningococcal vaccine coverage between the groups. Questionnaires in English and Arabic were completed to record the pilgrims' demographics and vaccination histories.

The British pilgrims, aged 14–81 years, all said they had been vaccinated. Of the 109 pilgrims from Saudi Arabia (aged 16–85 years), 70 (64%) reported being vaccinated, 35 (32%) stated they had not, and four (4%) were unsure. Fewer expatriates (43%) had been immunised than native Saudis (78%), but only 50% of pilgrims from Mecca and Jeddah had been immunised compared with 71% of those from the rest of the country.

The lower vaccine coverage in Saudi Arabia pilgrims overall, and Mecca's native residents in particular, is worrying and could lead to further meningococcal outbreaks. It also indicates the need for regular audit of the immunisation programme, and an investigation into why uptake is so low. Chemoprophylaxis (eg, with oral ciprofloxacin) might need to be reintroduced to clear infection from those carrying the bacteria and interrupt its spread.[3–5]

We declare that we have no conflict of interest. We also thank Elizabeth Haworth and Robert Booy, members of the Health at Hajj and Umra Research Group, for their contribution to this manuscript.

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Gastrointestinal safety of NSAIDs versus COX-2 inhibitors

Loren Laine and colleagues (Feb 10, p 465)[1] compare the upper gastrointestinal safety of the traditional non-steroidal anti-inflammatory drug (NSAID) diclofenac with that of the new cyclo-oxygenase-2 (COX-2) inhibitor etoricoxib. While matching the baseline characteristics of the two groups, certain factors have been overlooked.

Alcohol consumption has been associated with the risk of upper gastrointestinal bleeding in previous studies,[2] as have commonly prescribed antidepressants (serotonin-selective reuptake inhibitors), especially when used in combination with aspirin.[3]

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Helicobacter pylori, along with NSAIDs, is one of the major causes of peptic ulcer disease, and the two can have an additive effect. There is therefore the potential to introduce bias while assessing NSAID-associated peptic ulcer disease.[3,4] As has been suggested previously,[5] such bias could have been avoided by recruiting exclusively *H-pylori*-negative patients.

Appropriate stratification for these factors is essential before assessing the data and interpreting the statistical analysis.

I declare that I have no conflict of interest.

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Authors' reply

Amitabh Parashar suggests that "appropriate stratification" for alcohol, serotonin-selective reuptake inhibitors (SSRIs), and *Helicobacter pylori* is essential before analysing and interpreting our data on upper gastrointestinal events. Stratification for specific features is generally done for only the one or two most important risk factors. None of the characteristics mentioned by Parashar is an important risk factor for the primary endpoint of the MEDAL Program—cardiovascular events—nor are they the key risk factors for upper gastrointestinal events in users of non-steroidal anti-inflammatory drugs (NSAIDs).

Luckily, in very large trials, "randomisation works", and baseline characteristics are extremely well balanced between study groups. This is illustrated by the 34 701-person MEDAL Program. Every one of the 80 baseline characteristics assessed had a difference of less than 1% between treatment groups.

Intake of 14 or more alcoholic drinks per week was an exclusion criterion in the MEDAL Program, so heavy alcohol use was not an issue. Furthermore, alcohol use has not been identified as a predictor of upper gastrointestinal clinical events in large prospective gastrointestinal outcome trials in NSAID users,[1,2] nor in most NSAID observational studies. The two treatment groups in MEDAL were equally matched in terms of SSRI use (etoricoxib 7·6%; diclofenac 7·7%). And although *H pylori* is an independent risk factor for ulcers and ulcer bleeding, it was not a risk factor for upper gastrointestinal events in NSAID users in a large prospective outcomes trial,[2] nor did it increase the risk of ulcers in two large 12-week double-blind endoscopic trials in NSAID users.[3,4]

We wished to examine a broad range of patients representing "real-world" practice. Since most of the world's population has *H pylori* infection, restricting our population to *H-pylori*-negative patients would have run counter to that goal. Furthermore, accurate assessment of *H pylori* would be difficult in this multinational programme. The accuracy of antibody testing is relatively poor and varies widely from location to location around the world. Stool or breath testing has acceptable accuracy but proton-pump inhibitors (used by 39% of patients at baseline) cause a high rate of false-negative results.

We declare that we have no conflict of interest other than those stated in the original paper.

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In their Comment on cyclo-oxygenase (COX)-2 inhibitors and gastroprotection (Feb 10, p 439),[1] Joost Drenth and Freek Verheugt address the issue of the greater safety of these drugs compared with the combination of standard non-steroidal anti-inflammatory drugs (NSAIDs) and proton-pump inhibitors (PPIs). They conclude that the idea is a mere hypothesis which needs to be confirmed by a specific trial. To the best of my knowledge there are at least two clinical studies devoted to the matter.

Chan and colleagues[2] randomly assigned 287 *Helicobacter-pylori*-negative patients with previous ulcer bleeding to a 6-month therapeutic regimen with either celecoxib 200 mg twice daily plus once-daily placebo or a combination of diclofenac 75 mg twice daily plus once-daily omeprazole 20 mg. The probability of recurrent bleeding (4·9% and 6·4%, respectively) and the incidence of renal adverse effects were similar in both treatment groups.

More recently, Lai and colleagues[3] compared the efficacy in preventing ulcer relapses of either celecoxib 200 mg daily or a combination of naproxen 750 mg daily plus lansoprazole 30 mg daily in a group of 224 patients with a history of NSAID-related ulcers. Again, the two therapeutic regimens proved to be equally effective in preventing recurrent ulcer complications, the only significant difference being—not unexpectedly—a reduction in the occurrence of dyspepsia in patients treated with lansoprazole.

Obviously additional studies are warranted to confirm the above findings, but from the available data it seems that the use of a COX-2 inhibitor and the combination of an NSAID and a PPI represent two distinct but comparable options to reduce the frequency of ulcer complications induced by anti-inflammatory treatment.

The choice between the two regimens seems to rely mainly on the cost of therapy, which can vary between countries, and on the availability of generic PPIs.

I declare that I have no conflict of interest.

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Authors' reply

We concluded that the MEDAL Program provides interesting data, but falls short of answering the question of whether cyclo-oxygenase (COX)-2 inhibitors are safer than proton-pump inhibitors (PPIs) added to standard non-steroidal anti-inflammatory drugs (NSAIDs) in patients with osteoarthritis and rheumatoid arthritis.

Mario Guslandi indicates that at least two trials have compared COX-2 inhibition with PPI plus traditional NSAID with respect to gastrointestinal safety.[1,2] These two trials provide evidence that both regimens are comparable in terms of preventing recurrent ulcer complications. Let us first highlight the issues at stake here.

Randomised controlled trials by their very nature focus on a selective population and strictly define the outcome variable. The conclusions from these trials are, in sensu stricto, only applicable to populations with a similar clinical phenotype to that selected for the study. Both studies Guslandi mentions are from Hong Kong and studied patients with a very high gastrointestinal risk. In the study by Chan and colleagues,[1] patients were randomised after a previous peptic ulcer bleed, and in the one by Lai and colleagues[2] the primary outcome was also recurrent ulcer incidence. So, these patients have a different gastrointestinal risk profile to those included in the MEDAL Program.[3] This thwarts comparison between the MEDAL Program and the cited randomised trials.

The MEDAL Program recognised the issue and aimed to study the "real-world" situation. Patients were allowed to use aspirin or PPIs during the study period, but this lofty approach introduced confounding by indication. Indeed, the MEDAL Program allowed patients with the highest risk of gastrointestinal toxicity to use PPIs. These patients are likely to be systematically different from those not treated.

The ideal controlled trial would include patients with osteoarthritis and rheumatoid arthritis randomised to all possible combinations of COX-2 inhibitors, NSAIDs, PPIs, and aspirin. Serious cardiac or gastrointestinal events should be the primary outcome and dyspepsia might be used as a secondary outcome. Although it is difficult to foresee the result of such a trial, one might envisage that a PPI-based group has some advantages because PPIs decrease dyspepsia. Given the fact that the rate of dyspepsia in the target population is high and that it decreases compliance, a PPI-based treatment might possibly be the most effective strategy.[4]

JPHD and MGHvO have no conflict of interest to declare. FWAV has served on the clinical event committee of a coxib trial sponsored by Novartis.

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Taiwan–China health partnership is urgently needed for all

Your recent coverage of health in east Asia[1,2] is a timely reminder of the challenges to health posed by the political situation in this region, where the opening of markets brings both opportunities and risks. In the few years since China and Taiwan acceded to the World Trade Organization (WTO), in 2002, there has been a marked increase in the number of unsafe medicinal and food products appearing on the Taiwanese market.[3] This is a new phenomenon: Taiwan has, for many years, implemented the good manufacturing practice international

standard. In late 2006, more than 10 000 patients were found to have been prescribed counterfeit antihypertension drugs. Subsequent checks have revealed the presence of many more illegally produced medicines in Taiwanese pharmacies, at least some of which originate from China.

It is not only goods, but also people that cross borders. At present, more than 1 million Taiwanese work in other countries of east Asia, more than 80% of whom are in China. Taiwan's universal health insurance, established in 1995,[4] provides coverage for its citizens wherever treated. Yet there have been repeated concerns about the standards of care provided to our citizens in some Chinese hospitals. However, we have no mechanism by which to alert the Chinese authorities of our concerns. We are also concerned that our citizens might be tempted to take advantage of the trade in organs of executed prisoners.[5]

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However, our greatest concern is the potential offered to micro-organisms by travel between China and Taiwan. In late 2005, dead birds infected with the influenza A H5N1 virus were detected in flocks being smuggled from China to Taiwan. The growing volume of tourist and commercial flows pose challenges to both Taiwan and China.

In May last year, on the eve of the 59th World Health Assembly, I travelled to Geneva to seek support for Taiwan's membership of the WHO. I see this as essential if Taiwan is to play a full part in the implementation of the revised International Health Regulations, given the ongoing threat of an avian flu pandemic. My request for a meeting with my counterpart, Gao Qiang, the health minister of China, was not granted, even though I believe that we can both benefit from collaboration to tackle our shared concerns.

The international community has recognised the importance of including China and Taiwan in the global economy, by permitting them both to join the WTO. As *The Lancet* has noted, it is unfortunate that it does not place the same emphasis on global health. Taiwan stands ready to play its part.

I declare that I have no conflict of interest.

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Legal limits for paracetamol sales

Syed Rizwanuddin Ahmad (Feb 10, p 462)[1] notes that the US Food and Drug Administration continues to have concerns about the safety of paracetamol and that paracetamol overdose causes about 450 deaths in the USA every year.[2] There is strong evidence that restricting the availability of paracetamol reduces morbidity and mortality from paracetamol overdose.[3]

In Ireland, there were 7933 recorded cases of drug overdose in 2004, of which 31% involved paracetamol.[4] It is against the law for pharmacies in Ireland to sell more than 24 paracetamol (500 mg) tablets in a single transaction.[5] In early 2007, we visited 20 pharmacies in Dublin and attempted to purchase amounts of paracetamol in excess of this legal limit: ten pharmacies allowed us to do so.

In one pharmacy, staff hesitated before selling the tablets and afterwards admitted that they knew they were breaching regulations. Their explanation for going through with the sale to one of us was "you don't look like you'll kill yourself". In this case, their prediction was correct, but, at a population level, regulations must be uniformly enforced if they are to be effective.

We declare that we have no conflict of interest.

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Sluggish sperms

Shalender Bhasin and colleagues (Feb 17, p 597)[1] mention that hypothyroidism can cause female infertility.

Some years ago a member of hospital staff told me that he and his wife had been investigated for infertility. The only abnormality found had been "sluggish sperms". Clinically he was plainly hypothyroid and this was confirmed with tests. 3 months after starting thyroxine his wife became pregnant.

Sluggish sperms associated with hypothyroidism might not be a common cause of infertility, but when assessing thyroid function in infertile men it should be remembered.

I declare that I have no conflict of interest.

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The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL Study): an open-label randomised comparison

*David G Sherman, Gregory W Albers, Christopher Bladin, Cesare Fieschi, Alberto A Gabbai, Carlos S Kase, William O'Riordan, Graham F Pineo, on behalf of the PREVAIL Investigators**

Summary

Background Venous thromboembolism prophylaxis with low molecular weight heparin or unfractionated heparin is recommended in acute ischaemic stroke, but which regimen provides optimum treatment is uncertain. We aimed to compare the efficacy and safety of enoxaparin with that of unfractionated heparin for patients with stroke.

Methods 1762 patients with acute ischaemic stroke who were unable to walk unassisted were randomly assigned within 48 h of symptoms to receive either enoxaparin 40 mg subcutaneously once daily or unfractionated heparin 5000 U subcutaneously every 12 h for 10 days (range 6–14). Patients were stratified by National Institutes of Health Stroke Scale (NIHSS) score (severe stroke ≥14, less severe stroke <14). The primary efficacy endpoint was the composite of symptomatic or asymptomatic deep vein thrombosis, symptomatic pulmonary embolism, or fatal pulmonary embolism. Primary safety endpoints were symptomatic intracranial haemorrhage, major extracranial haemorrhage, and all-cause mortality. This study is registered with ClinicalTrials.gov, number NCT00077805.

Findings In the efficacy population (ie, one or more dose received, presence of deep vein thrombosis or pulmonary embolism, or assessment for venous thromboembolism), enoxaparin (n=666) and unfractionated heparin (669) were given for 10·5 days (SD 3·2). Enoxaparin reduced the risk of venous thromboembolism by 43% compared with unfractionated heparin (68 [10%] *vs* 121 [18%]; relative risk 0·57, 95% CI 0·44–0·76, p=0·0001; difference –7·9%, –11·6 to –4·2); this reduction was consistent for patients with an NIHSS score of 14 or more (26 [16%] *vs* 52 [30%]; p=0·0036) or less than 14 (42 [8%] *vs* 69 [14%]; p=0·0044). The occurrence of any bleeding was similar with enoxaparin (69 [8%]) or unfractionated heparin (71 [8%]; p=0·83). The frequency of the composite of symptomatic intracranial and major extracranial haemorrhage was small and closely similar between groups (enoxaparin 11 [1%] *vs* unfractionated heparin 6 [1%]; p=0·23). We noted no difference for symptomatic intracranial haemorrhage between groups (4 [1%] *vs* 6 [1%], respectively; p=0·55); the rate of major extracranial bleeding was higher with enoxaparin than with unfractionated heparin (7 [1%] *vs* 0; p=0·015).

Interpretation Our results suggest that for patients with acute ischaemic stroke, enoxaparin is preferable to unfractionated heparin for venous thromboembolism prophylaxis in view of its better clinical benefits to risk ratio and convenience of once daily administration.

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Introduction

Stroke is a major health problem that is growing in importance.[1] WHO estimates that 15 million people have a stroke every year, and this number is rising.[2] Each year in the USA alone, 700 000 people have a first or recurrent stroke,[3] 88% of which are ischaemic. Stroke is also the third most common cause of death and the leading cause of disability in adults.[4,5]

Venous thromboembolism is a common but preventable complication of acute ischaemic stroke, and is associated with increased mortality and long-term morbidity and substantial health-care costs for its management.[6] The risk of venous thromboembolism for patients who have had an acute ischaemic stroke is close to that for patients undergoing major surgical procedures.[6] Without venous thromboembolism prophylaxis, up to 75% of patients with hemiplegia after stroke develop deep vein thrombosis and 20% develop pulmonary embolism,[7,8] which is fatal in 1–2% of patients with acute ischaemic stroke and causes up to 25% of early deaths after strokes.[9]

The benefits of prophylaxis have been seen in patients with acute ischaemic stroke, and low molecular weight heparin and unfractionated heparin are therefore recommended in guidelines from expert consensus groups.[10–14] For physicians to select the most appropriate prophylactic regimen, they need to decide which will achieve maximum reduction of venous thromboembolism risk while keeping the risk of bleeding to a minimum. Up to now, small-scale studies have suggested that low molecular weight heparin is better than or equivalent to unfractionated heparin for prevention of venous thromboembolism after acute ischaemic stroke,[15,16] but these studies were restricted in their ability to assess the benefit to risk ratio of the prophylactic treatments.

***Panel:* Patient exclusion criteria**

- Evidence of VTE at screening or evidence of active bleeding
- Evidence or history of intracranial haemorrhage, heparin-induced or enoxaparin-induced thrombocytopenia or thrombosis, or both
- Hypersensitivity to iodinated contrast media or iodine
- Spinal or epidural analgesia or lumbar puncture within the preceding 24 h
- Thrombolytic treatment within the preceding 24 h
- Comatose at screening (NIHSS score ≥2 for level of consciousness)
- Known or suspected cerebral aneurysm or arteriovenous malformation
- Confirmed malignant disease that might have posed an increased risk for bleeding or compromise follow-up or outcome assessment
- Impaired haemostasis, such as baseline platelet count <100 000 per μL, aPTT 1·5-times the laboratory upper limit of normal, or INR >1·5
- Major surgery or major trauma within the preceding 3 months
- Expected need for full-dose treatment with therapeutic levels of an anticoagulant
- Treatment with LMWH or UFH at a prophylactic dose for more than 48 h before inclusion
- Allergy or known hypersensitivity to heparin or enoxaparin
- Bacterial endocarditis
- Prosthetic heart valve
- Known or suspected severe anaemia (haemoglobin <100 g/L)
- Uncontrolled arterial hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg) at randomisation or clinical hypertensive urgency
- Life expectancy less than 3 months due to comorbid disorders
- Participation in another clinical study within the preceding 30 days
- Any clinically relevant serious diseases, including severe liver disease or renal failure (creatinine clearance <30 mL/min on at least two occasions)
- Female patients were not enrolled if they were breastfeeding, pregnant, or could become pregnant during the study.

aPTT=activated partial thromboplastin time. LMWH=low molecular weight heparin. INR=international normalised ratio. NIHSS=National Institutes of Health Stroke Scale. UFH=unfractionated heparin. VTE=venous thromboembolism.

A meta-analysis showed that low molecular weight heparin and heparinoids reduce the risk of deep vein thrombosis and symptomatic pulmonary embolism by around two-thirds compared with placebo or no treatment, with a two-fold increase in the risk of extracranial bleeding.[17] Meta-analyses of low-dose and high-dose low molecular weight and unfractionated heparin regimens have suggested that low-dose low molecular weight heparin could provide the best benefit to risk ratio in patients with acute ischaemic stroke by decreasing the risk of both deep vein thrombosis and pulmonary embolism without increasing the risk of intracranial or extracranial haemorrhage.[18,19] However, in one meta-analysis the investigators warn against drawing conclusions on the basis of haemorrhagic complications because of the low numbers of events.[18] Nevertheless, prophylactic regimens used for patients with stroke are quite varied because many physicians remain uncertain about the best treatment, and data from studies with high numbers of patients are needed to resolve this issue.

We have therefore done a large scale, multinational, randomised study to compare the efficacy and safety of the low molecular weight heparin enoxaparin with that of unfractionated heparin for venous thromboembolism prophylaxis in patients with acute ischaemic stroke.

Methods

Patients

Patients were eligible for enrolment if they were 18 years or older with an acute ischaemic stroke confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) and unable to walk unassisted because of motor impairment, with a score of 2 or more as indicated by National Institutes of Health Stroke Scale (NIHSS)[20] for motor function of the leg. Onset of stroke symptoms had to have occurred within 48 h before randomisation. The panel shows exclusion criteria.

All patients provided written informed consent. The study was done according to the Declaration of Helsinki and local regulations. Approval to do the study was obtained from the institutional review board at all sites.

Study design

Eligible patients were stratified according to severity of the index stroke and then randomised on a 1 to 1 basis, with permuted blocks of four, within each of two strata: severe strokes (NIHSS score ≥14) and less severe strokes (NIHSS score <14). The sponsor generated the randomisation schedule that was implemented centrally by an independent interactive voice-response system.

Within 48 h of the onset of stroke symptoms, patients received either enoxaparin 40 mg subcutaneously once daily or unfractionated heparin 5000 U subcutaneously every 12 h for 10 days (range 6–14). Study treatment was not blinded.

The primary efficacy endpoint was the cumulative occurrence of confirmed venous thromboembolism, defined as the composite of symptomatic or asymptomatic deep vein thrombosis, or symptomatic or fatal pulmonary embolism during the study treatment phase (up to day 14). All patients had deep vein thrombosis confirmed by bilateral contrast venography at the end of the treatment period, with the exception of patients for whom this method was not practical, and

ultrasonography was used to confirm deep vein thrombosis. Pulmonary embolism was confirmed by ventilation perfusion (VQ) or thoracic helical CT scan, or pulmonary angiography. Fatal pulmonary embolism was confirmed by autopsy. If deep vein thrombosis in an upper or lower limb or pulmonary embolism was suspected during treatment, a diagnostic algorithm was followed. For symptomatic deep vein thrombosis, compression ultrasonography (B-mode or duplex scan) of the veins of the affected limb was done within 48 h of symptom onset. A positive diagnosis of thrombosis was made on the basis of direct visualisation of the thrombus and incompressibility of the affected vein segment. Contrast venography was done with either the long-leg method[21] or the Rabinov and Paulin method[22] if an ultrasound scan was not diagnostic.

If symptomatic pulmonary embolism was suspected, a VQ lung scan was undertaken and interpreted on the basis of the standards published in the Prospective Investigation of Pulmonary Embolism Diagnosis.[23] If the results suggested an intermediate probability of pulmonary embolism or were uninterpretable, a further examination was done to confirm or reject the diagnosis, preferably with thoracic helical CT scan or pulmonary angiography, or both, or compression ultrasonography examination of the veins of the leg or a bilateral ascending venography of the legs, or both. In bilateral ascending venography, detection of a deep vein thrombosis in the legs associated with signs suggestive of pulmonary embolism led to confirmation of the diagnosis.

Secondary efficacy endpoints were occurrence of objectively verified symptomatic venous thromboembolism (deep vein thrombosis or pulmonary embolism, or both) at 30, 60, and 90 days from the time of randomisation; stroke recurrence within the study treatment period and at 30, 60, and 90 days after randomisation; stroke progression during the study treatment period identified by an increase in NIHSS score of 4 or more points from the highest previous score obtained at baseline or during study treatment that is due to additional new areas of focal brain ischaemia; NIHSS scores at days 4, 7, 10, and 14 during admission to hospital, at end of study treatment, and at the 30-day and 90-day follow-up; and modified Rankin scale scores at end of study treatment and at the 30-day and 90-day follow-up visits.

The primary safety endpoints were symptomatic intracranial haemorrhage, major extracranial haemorrhage, and all-cause mortality up to 48 h after treatment. Intracranial haemorrhages were verified by head CT scan, brain MRI scan, or autopsy, and were classified, on the basis of scan results and the patient's clinical presentation, as asymptomatic haemorrhagic transformation, symptomatic haemorrhagic transformation, primary intracerebral haemorrhage, subarachnoid haemorrhage, or subdural or epidural haemorrhage. Major extracranial haemorrhage was defined as overt bleeding resulting either in death, drop in haemoglobin concentration of 30 g/L or more, need for transfusion of two or more units of blood, surgical intervention or decompression of closed space to stop or control the event, or bleeding in a retroperitoneal or intraocular location. Clinically important bleeding was defined post hoc as the composite of symptomatic intracranial and major extracranial haemorrhages.

Secondary safety endpoints included minor extracranial haemorrhage, thrombocytopenia, and adverse events. Minor extracranial haemorrhage was defined as any clinically overt bleeding not meeting the criteria for major extracranial haemorrhage, and associated with at least one of the following: epistaxis lasting more than 5 min or needing intervention, ecchymosis or haematoma larger than 5 cm at its widest point,

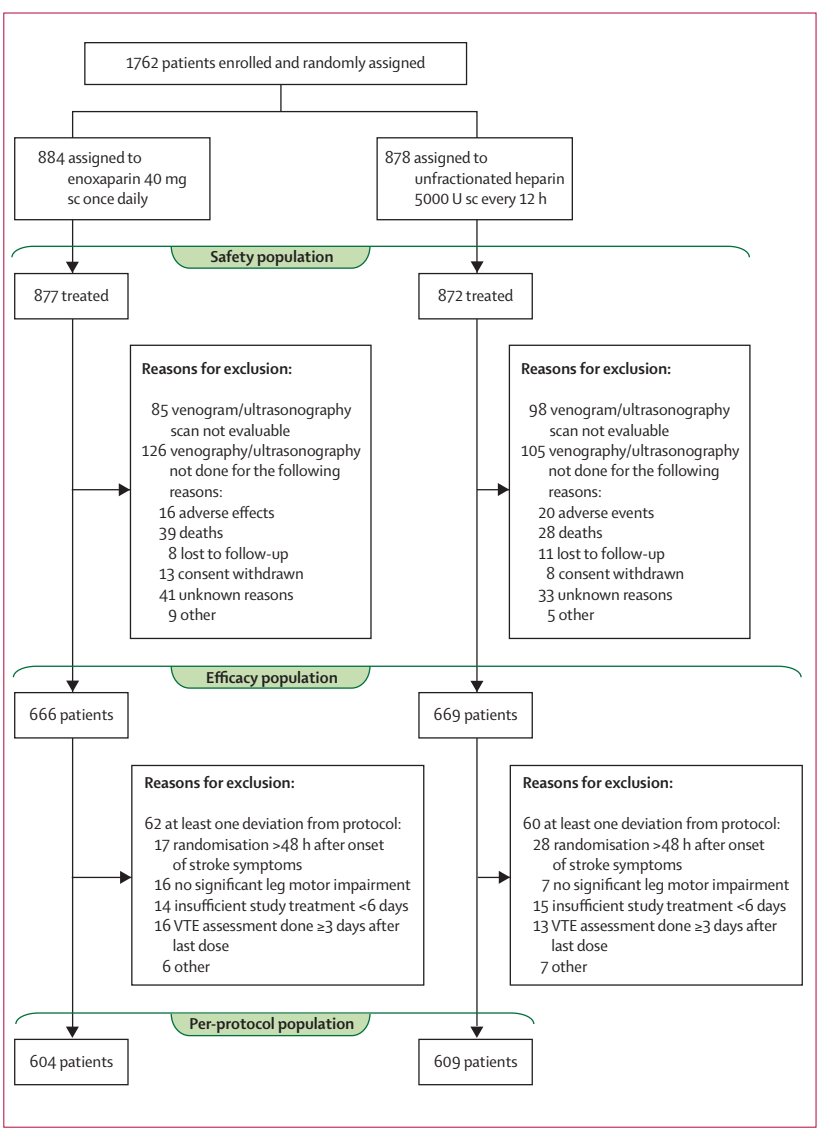


Figure 1: **Trial profile**
VTE=venous thromboembolism. sc=subcutaneously.

	Enoxaparin (n=884)	Unfractionated heparin (n=878)
Age (years)	65·9 (12·9)	66·1 (12·9)
<65	371 (42%)	372 (42%)
65–75	312 (35%)	265 (30%)
>75	201 (23%)	241 (27%)
Male patient	521 (59%)	473 (54%)
Body-mass index (kg/m²)	27·0 (5·3)	27·0 (5·3)
≥30	179 (20%)	183 (21%)
Race		
White	523 (59%)	523 (60%)
Black	68 (8%)	55 (6%)
Asian	182 (21%)	193 (22%)
Hispanic	73 (8%)	68 (8%)
Others	38 (4%)	39 (4%)
NIHSS score	11·3 (5·1)	11·3 (5·1)
<14	648 (73%)	626 (71%)
≥14	236 (27%)	252 (29%)
Motor leg function (NIHSS score)		
0	3 (<1%)	0
1	16 (2%)	10 (1%)
2	356 (40%)	381 (43%)
3	316 (36%)	293 (33%)
4	193 (22%)	387 (22%)
Risk factors for VTE		
Venous stasis syndrome	3 (<1%)	11 (1%)
Varicosis	19 (2%)	16 (2%)
Previous VTE	16 (2%)	14 (2%)
Risk factors for stroke		
Diabetes	266 (30%)	270 (31%)
Previous stroke	246 (28%)	249 (28%)
Hyperlipidaemia	70 (8%)	68 (8%)
Hypertension	621 (70%)	637 (73%)
Previous thrombolytic therapy	50 (6%)	58 (7%)
Concomitant antiplatelet therapy	815 (92%)	791 (90%)
Aspirin	767 (87%)	738 (84%)
Aspirin with dipyridamole	36 (4%)	45 (5%)
Clopidogrel	189 (21%)	174 (20%)
Dipyridamole	40 (5%)	47 (5%)
Ticlopidine	28 (3%)	28 (3%)
Other	52 (6%)	56 (6%)

Data are number (%) or mean (SD). NIHSS=National Institutes of Health Stroke Scale. VTE=venous thromboembolism.

Table 1: **Baseline characteristics**

haematuria not associated with urinary catheter trauma, gastrointestinal haemorrhage not related to intubation or nasogastric tube placement, wound haematoma or haemorrhagic wound complications not associated with features of overt haemorrhage classified as major, or subconjunctival haemorrhage needing end of study treatment.

A steering committee was responsible for the design of the study, modifications to the study protocol, and blinded adjudication of major haemorrhage events. A central adjudication committee did a blinded review of all images, including venograms, ultrasound, CT and VQ scans, and angiograms, and an independent data safety monitoring board ensured the proper conduct of the study and undertook four blinded safety data reviews before the database was locked. No modifications to the study protocol were recommended by the data safety monitoring board during the study.

Statistical analysis

The sample size was determined by assumption of a frequency of venous thromboembolism at day 14 of 20% in the unfractionated heparin group and 14% in the enoxaparin group, resulting in a 30% relative risk reduction in patients receiving enoxaparin compared with those receiving unfractionated heparin. To detect the treatment difference at the 5% (two-sided) level of significance with 80% power, and assuming an attrition rate of 30%, about 880 patients per treatment group (1760 in total) were needed.

The efficacy population was defined a priori as all randomly assigned patients who had taken one or more dose of study medication; had proven deep vein thrombosis or pulmonary embolism, or both; or had one or more contrast venography or ultrasonography assessment for venous thromboembolism during the study treatment period (10 days [range 6–14]). Venous thromboembolism assessment was allowed up to 72 h after the end of treatment; therefore, 17 days was the maximum time allotted for the final assessment. The primary outcome was also analysed in a per-protocol efficacy population consisting of all efficacy population patients who had no major protocol violations. The safety population included all patients who had taken one or more dose of study medication.

The primary efficacy analysis was done with the Cochran-Mantel-Haenszel statistic with baseline NIHSS risk group (low-risk group with NIHSS < 14 *vs* high-risk group with NIHSS ≥ 14) as the stratification factor. The blinded adjudicated data for venous thromboembolism were used in the analysis. χ^2 test or Fisher's exact test were used for unadjusted treatment comparisons. Time-to-event analysis for all-cause mortality was done with Cox proportional hazards model. Analyses were done with SAS statistical software (version 8.2).

This study is registered with ClinicalTrials.gov, number NCT00077805.

Role of the funding source

The protocol was written by the steering committee and revised on the basis of discussions with the sponsor (Sanofi-Aventis, Paris, France). Data were obtained by the sponsor, and data entry was undertaken by a contract research organisation (Parexel, Waltham, MA, USA). The data were maintained by the contract research organisation and analysed by the sponsor according to the statistical

	Enoxaparin (n=666)	Unfractionated heparin (n=669)	Relative risk (95% CI)*	p†	Difference (95% CI)
VTE	68 (10%)	121 (18%)	0·57 (0·44–0·76)	0·0001	–7·9% (–11·6 to –4·2)
PE‡	1 (<1%)	6 (1%)	0·17 (0·02–1·39)	0·059	–0·7% (–1·5 to 0)
Symptomatic VTE	2 (<1%)	7 (1%)	0·29 (0·06–1·38)	0·096	–0·7% (–1·6 to 0·1)
Symptomatic DVT	1 (<1%)	4 (1%)	0·25 (0·03–2·24)	0·18	–0·4% (–1·1 to 0·2)
Asymptomatic DVT§	66 (10%)	114 (17%)	0·57 (0·43–0·75)	<0·0001	–7·1% (–10·8 to –3·5)
All DVT	67 (10%)	118 (18%)	0·57 (0·43–0·75)	<0·0001	–7·6% (–11·3 to –3·9)
Proximal	30 (5%)	64 (10%)	0·47 (0·31–0·72)	0·0003	–5·1% (–7·8 to –2·3)
Distal	44 (7%)	85 (13%)	0·52 (0·37–0·74)	0·0002	–6·1% (–9·2 to –2·9)
Proximal and distal¶	7 (1%)	31 (5%)	0·23 (0·10–0·51)	<0·0001	–3·6% (–5·4 to –1·8)

Data are number (%) unless otherwise indicated. DVT=deep vein thrombosis. PE=pulmonary embolism. VTE=venous thromboembolism. The individual numbers of events for each endpoint do not always add up to the total number because patients might have had more than one type of event. *Enoxaparin versus unfractionated heparin. †Adjusted for National Institutes of Health Stroke Scale score stratification for VTE, but unadjusted for other criteria. ‡Three PE events were fatal (one with enoxaparin and two with unfractionated heparin). §Confirmed by ultrasound: five of 66 (8%) enoxaparin, nine of 114 (8%) unfractionated heparin; confirmed by venography: 61/66 (92%) enoxaparin, 104/114 (91%) unfractionated heparin. ¶Events also counted in proximal DVT and distal DVT.

Table 2: **Incidence of venous thromboembolic events up to day 14 in the efficacy group**

analysis plan, which was reviewed by the steering committee. The steering committee had full access to the data and vouches for its integrity and completeness. The statistician (MC) did all data analyses and vouches for the accuracy of the analyses. The steering committee was responsible for interpretation of the data and in the decision to submit for publication.

Results

In total, 1762 acute ischaemic stroke patients were randomly assigned between August, 2003, and April, 2006, at 200 centres in 15 countries (Australia, Austria, Brazil, Canada, Colombia, Czech Republic, India, Israel, Italy, South Korea, Mexico, Poland, South Africa, Turkey, and USA). Figure 1 shows the trial profile. Of the randomised patients, 13 (seven in enoxaparin group and six in unfractionated heparin group) did not receive study treatment and were not included in the safety or efficacy populations. A further 414 patients (211 in enoxaparin group and 203 in unfractionated heparin group) were not included in the efficacy population. The primary outcome was assessed in 1096 (82%) patients by venography alone (41% in both treatment groups), 182 (14%) by ultrasonography alone (7% in both groups), and 49 (4%) with both venography and ultrasonography (2% in both groups). The mean time until venography was 10·5 days (SD 3·2) in each group.

Table 1 shows baseline characteristics. In the efficacy population, the mean duration of prophylaxis was 10·5 days (3·2) for both treatment groups. The mean duration from index stroke to initiation of prophylaxis was 1·2 days (0·8) for enoxaparin and 1·2 days (0·7) for unfractionated heparin. In both groups, a similar number of patients received either aspirin or platelet inhibitors, or both, for more than 6 days after randomisation (726 [82%] with enoxaparin and 698 [80%] with unfractionated heparin).

Enoxaparin significantly reduced the frequency of venous thromboembolism in the efficacy population at day 14 compared with unfractionated heparin (relative risk [RR] reduction 43%; difference –7·9%, 95% CI –11·6 to –4·2; table 2). Similar results were seen in the per-protocol population (62 [10%] *vs* 112 [18%], respectively;

	NIHSS score <14		NIHSS score ≥14	
	Occurrence (95% CI)	p	Occurrence (95% CI)	p
VTE				
Enoxaparin	8·3% (5·90–10·70)	0·004	16·3% (10·53–21·97)	0·004
UFH	14·0% (10·91–17·02)		29·7% (22·94–36·49)	
DVT				
Enoxaparin	8·1% (5·73–10·48)	0·005	16·3% (10·53–21·97)	0·005
UFH	13·6% (10·54–16·58)		29·1% (22·41–35·88)	

UFH=unfractionated heparin.

Table 3: **Occurrence of venous thromboembolism (VTE) and deep vein thrombosis (DVT) according to National Institutes of Health Stroke Scale (NIHSS)**

	NIHSS score <14		NIHSS score ≥14	
	Occurrence (95% CI)	p	Occurrence (95% CI)	p
Total				
Enoxaparin	6·2% (4·34 to 8·06)	0·96	12·5% (8·24 to 16·76)	0·97
UFH	6·3% (4·36 to 8·18)		12·4% (8·31 to 16·49)	
Clinically significant intracranial				
Enoxaparin	0·3% (–0·12 to 0·74)	0·97	0·9% (–0·33 to 2·05)	0·47
UFH	0·3% (–0·12 to 0·77)		1·6% (0·04 to 3·16)	
Major extracranial				
Enoxaparin	0·5% (–0·06 to 0·99)	0·09	1·7% (0·05 to 3·40)	0·04
UFH	0		0	
Clinically important				
Enoxaparin	0·8% (0·10 to 1·45)	0·28	2·6% (0·54 to 4·63)	0·45
UFH	0·3% (–0·12 to 0·77)		1·6% (0·04 to 3·16)	

Clinically important bleeding is defined as the composite of major extracranial and symptomatic intracranial haemorrhages. UFH=unfractionated heparin.

Table 4: **Occurrence of haemorrhage according to National Institutes of Health Stroke Scale (NIHSS)**

RR 0·56, 0·42–0·75, p=0·0001; difference –8·1%, –12·0 to –4·2). The relative reduction of risk of venous thromboembolism seen with enoxaparin, compared with unfractionated heparin, was maintained at day 30 (70 [11%] *vs* 121 [18%], p<0·0001), day 60 (70 [11%] *vs* 122 [18%], p<0·0001), and at day 90 (70 [11%] *vs* 122 [18%], p<0·0001).

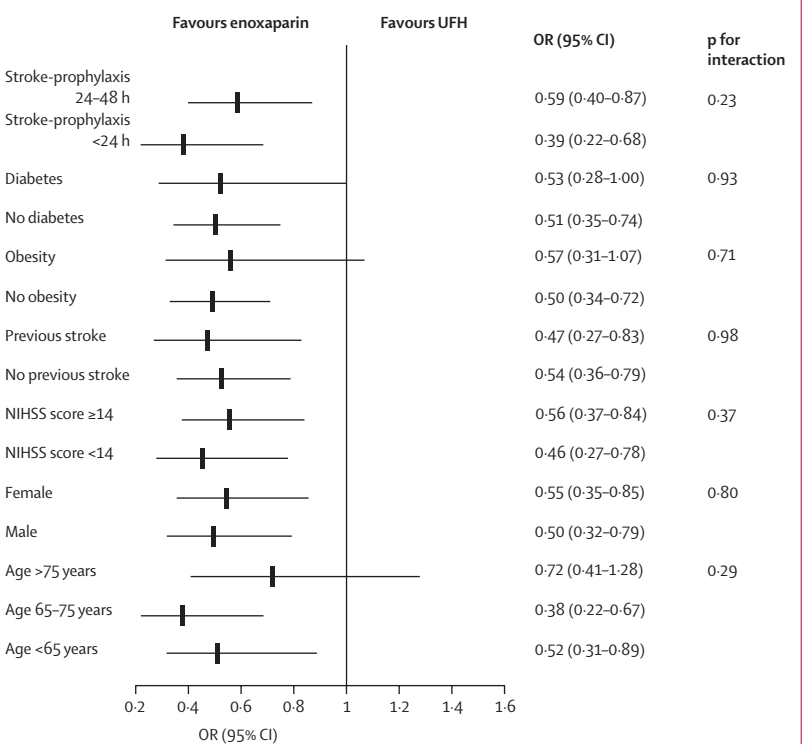


Figure 2: **Forest plot for risk for venous thromboembolism in patients with acute ischaemic stroke by patient characteristics for enoxaparin and unfractionated heparin**
NIHSS=National Institutes of Health Stroke Scale. OR=odds ratio. UFH=unfractionated heparin.

The reduction in the risk of venous thromboembolism with enoxaparin compared with unfractionated heparin at day 14 was consistent for both total deep vein thrombosis (RR reduction 43%) and proximal deep vein thrombosis (53%; table 2). There was a non-significant 83% reduction in the risk of pulmonary embolism (table 2).

The incidence of symptomatic venous thromboembolism did not significantly differ between the enoxaparin and unfractionated heparin groups at days 14 (table 2), 30 (one [0·2%] *vs* three [0·4%], p=0·62), 60 (one [0·2%] *vs* one [0·2%], p=1·0), and 90 (one [0·2%] *vs* 0, p=0·50).

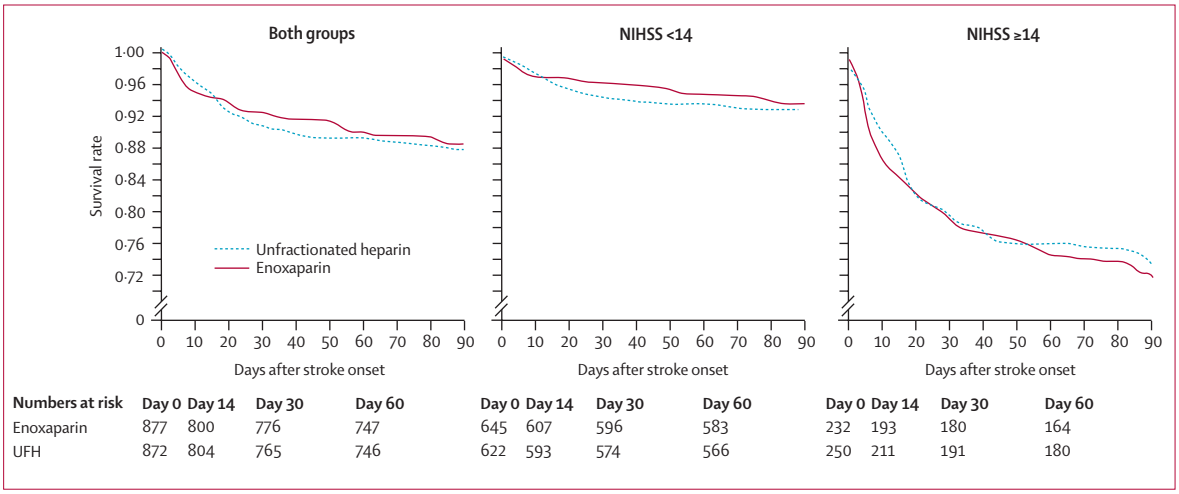
The occurrence of venous thromboembolism was higher for patients with an NIHSS score of 14 or more than for those with a score of less than 14 (table 3). Compared with unfractionated heparin, enoxaparin reduced the frequency of venous thromboembolism for patients with an NIHSS score less than 14 (RR 0·59, 95% CI 0·41–0·85, p=0·0043; difference –5·7%, –9·6 to –1·8%), and for those with an NIHSS score of 14 or more (0·55, 0·36–0·83, p=0·0036; difference –13·5%, –22·3 to –4·6; figure 2). A post-hoc analysis of the major subgroups showed consistent reductions of the risk of venous thromboembolism by enoxaparin compared with unfractionated heparin (figure 2).

The occurrence of any bleeding at the end of treatment plus up to 48 h afterwards was similar between groups (table 5). The frequency of symptomatic intracranial haemorrhage was also similar between groups, and the incidence of major extracranial haemorrhage was higher

	Enoxaparin (n=877)	Unfractionated heparin (n=872)	Relative risk (95% CI)	p*	Difference (95% CI)
Bleeding at end of treatment + 48 h					
Total†	69 (8%)	70 (8%)	0·98 (0·71–1·35)	0·90	–0·2% (–2·7% to 2·4)
Symptomatic intracranial haemorrhage	4 (1%)	6 (1%)	0·66 (0·19–2·34)	0·55	–0·2% (–0·9% to 0·5)
Death of patient with symptomatic intracranial haemorrhage	3 (<1%)	4 (1%)	..	..	–0·1% (–0·7% to 0·5)
Major extracranial haemorrhage‡	7 (1%)	0	..	0·015	0·8% (0·2% to 1·4)
Resulting in death	2 (<1%)	0	..	..	0·2% (–0·1% to 0·5)
Drop of haemoglobin ≥30 g/L	7 (1%)	0	..	..	0·8% (0·2% to 1·4)
Transfusion of ≥2 units of blood	5 (1%)	0	..	..	0·6% (0·1% to 1·1)
Clinically important haemorrhage	11 (1%)	6 (1%)	1·82 (0·68–4·91)	0·23	0·6% (–0·4% to 1·5)
Death of patient with clinically important haemorrhage§	5 (1%)	4 (1%)	1·24 (0·33–4·65)	1·0	0·1% (–0·6% to 0·8)
Minor extracranial haemorrhage¶	42 (5%)	48 (6%)	0·87 (0·58–1·30)	0·50	–0·7% (–2·8% to 1·4)
All-cause mortality up to day 14	48 (6%)	45 (5%)	1·12‖ (0·75–1·69)	0·58**	..
All-cause mortality up to day 90	100 (12%)	103 (12%)	1·01‖ (0·77–1·33)	0·96**	..

Data are number (%) unless otherwise indicated. *Fisher's exact test if n<6 in one group. χ^2 test if n≥6 in one group. †Some patients had more than one bleeding event. ‡Three were gastrointestinal bleeding, one surgical stoma of tracheostomy, one duodenal ulcer haemorrhage, one haematuria, and one haemoglobin decrease. §Defined as the composite of major extracranial and symptomatic intracranial haemorrhages. ¶All intracranial haemorrhages were regarded as major. ‖Hazard ratio. **Log-rank test.

Table 5: **Safety outcomes**



Numbers at risk	Day 0	Day 14	Day 30	Day 60	Day 0	Day 14	Day 30	Day 60	Day 0	Day 14	Day 30	Day 60
Enoxaparin	877	800	776	747	645	607	596	583	232	193	180	164
UFH	872	804	765	746	622	593	574	566	250	211	191	180

Figure 3: **Kaplan-Meier survival analysis in the enoxaparin and unfractionated heparin groups**
UFH=unfractionated heparin.

with enoxaparin than with unfractionated heparin (table 5). The incidence of clinically important haemorrhage was small and did not differ between groups. There were no differences in deaths of patients with clinically important haemorrhage between groups.

The occurrence of any bleeding was about two-fold higher for patients with a score of 14 or more than for those with a score less than 14 (table 4). No significant differences in the occurrence of any bleeding or symptomatic intracranial haemorrhage were noted between the enoxaparin and unfractionated heparin groups (table 4). There was a higher incidence of major extracranial haemorrhages in the enoxaparin group than in the unfractionated heparin group. This difference was significant for patients with an NIHSS score of 14 or more but not significant for those with an NIHSS score less than 14 (table 4). The incidence of clinically important haemorrhage was similar between the enoxaparin and unfractionated heparin groups (table 5).

All-cause mortality rate up to day 14 and 90 did not differ in the enoxaparin and unfractionated heparin groups (table 5). Kaplan-Meier analysis (figure 3) showed no differences in the survival of patients who received enoxaparin or unfractionated heparin, or for those with an NIHSS score less than 14 or 14 or more.

The rate of mortality for reasons other than venous thromboembolism, stroke, or haemorrhage was similar in the enoxaparin group (67 [8%]) and unfractionated heparin group (73 [8%]).

Discussion

We have shown that enoxaparin 40 mg subcutaneously once daily is significantly more effective than unfractionated heparin 5000 U subcutaneously every 12 h for the prevention of venous thromboembolism in patients with acute ischaemic stroke, and noted a consistent reduction in the risk of proximal deep vein thrombosis. The risk of pulmonary embolism was lower in patients receiving enoxaparin than in those receiving unfractionated heparin, although this difference was not significant. The magnitude of the risk reduction for venous thromboembolism was maintained at least up to 90 days.

The occurrence of symptomatic intracranial haemorrhage, a complication of major importance to physicians treating patients with acute ischaemic stroke, was similar between groups. Although the incidence of major extracranial haemorrhage was significantly higher in the enoxaparin group than in the unfractionated heparin group, these bleeding events, which were mainly gastrointestinal, did not lead to increased mortality. We also assessed clinically important bleeding, a combined endpoint defined post hoc to be used as a meaningful way for clinicians to adequately balance benefits and risks of treatment of patients with acute ischaemic stroke. Similar criteria have been used in several studies of venous thromboembolism prophylaxis.[24] There was a low frequency of clinically important bleeding with no significant difference between groups.

Although the occurrence of venous thromboembolism was about two-fold higher in patients with an NIHSS score of 14 or more than in those with a score less than 14 (in line with previous studies[25]), a similar reduction in venous thromboembolism risk with enoxaparin versus unfractionated heparin was noted in both groups of patients. This consistent reduction of risk was also seen in patients with acute ischaemic stroke and diabetes, obesity, a previous stroke, age younger than 65 years, 65–75 years, or older than 75 years, and was not dependent on sex. Importantly, a delay in initiation of prophylaxis for up to 48 h after the onset of stroke did not affect the reduction in venous thromboembolism risk with enoxaparin compared with unfractionated heparin.

Previous studies suggested that low molecular weight heparin was either at least as effective as, or more effective

than, unfractionated heparin for reduction of the risk of venous thromboembolism in patients with acute ischaemic stroke.[15,16] Our data confirm the preliminary observations reported by Hillbom and colleagues.[16] These investigators compared venous thromboembolism prophylaxis with a 40 mg once daily dose of enoxaparin versus unfractionated heparin 5000 IU three times daily in 212 acute ischaemic stroke patients. In the efficacy analysis (n=148), patients given enoxaparin had fewer venous thromboembolism events than did those receiving unfractionated heparin (20% *vs* 35%, absolute difference 15%, 95% CI 0·8–29·2, p=0·044). However, that study was not designed to show that enoxaparin is better than unfractionated heparin for reduction in venous thromboembolism risk. Furthermore, both studies used venography to screen for deep vein thrombosis and had a similar duration of prophylaxis (6–14 days). The overall mortality rate in Hillbom and co-workers' study[16] was higher than that reported in our study, which might partly be explained by improvement of patient care in recent years.

Diener and colleagues[15] showed that the frequency of a composite endpoint of proximal deep vein thrombosis, pulmonary embolism, or death related to venous thromboembolism did not differ significantly for patients with acute ischaemic stroke receiving certoparin 3000 U once daily compared with those receiving unfractionated heparin 5000 U thrice daily (7% *vs* 10%, p=0·0011 for non-inferiority). However, there were some notable differences in design between our study and that of Diener and co-workers.[15] The Diener study was not designed to show whether low molecular weight heparin was better than unfractionated heparin for prevention of venous thromboembolism, and used duplex or compression ultrasonography rather than venography for screening proximal deep vein thrombosis.[15] Additionally, the index stroke was less severe (mean baseline NIHSS score 8·2–8·8) than it was for patients in our study (mean baseline NIHSS score 11·3), and the duration of prophylaxis was longer (12–16 days).

A potentially important difference between the PREVAIL study and many of the previous trials was the choice of the unfractionated heparin dosing regimen. In previous studies,[15,16] a three times daily unfractionated heparin regimen was used, whereas we chose a twice daily regimen. After careful review of existing published work and the absence of a direct comparison of twice daily and three times daily unfractionated heparin regimens or precise guidance in international consensus guidelines, we selected a twice daily regimen. This decision was based on a meta-analysis showing that both regimens of the drug are effective in reducing the risk of venous thromboembolism compared with placebo or no prophylaxis (60% reduction in risk with unfractionated heparin twice daily and 72% three times daily),[26] and studies suggesting that unfractionated heparin three times daily might have a less favourable safety profile than has low molecular weight heparin.[27,28]

Hillbom's findings[16] also showed a trend towards more haemorrhagic transformation of acute ischaemic stroke in patients receiving unfractionated heparin thrice daily than in those receiving enoxaparin. As a result, physicians use varied prophylactic regimens for patients with stroke, including a twice daily unfractionated heparin regimen. Since this study did not compare low molecular weight heparin with unfractionated heparin thrice daily, the risk reduction for efficacy and safety for these prophylactic regimens is difficult to conclude, although there was a similar 43% relative risk reduction for venous thromboembolism in both our study and that of Hillbom.[16] On the basis of our data, the number needed to treat to avoid one venous thromboembolism is 13 whereas the number needed to harm as a result of clinically important bleeding is 173, showing a clear net clinical benefit in favour of enoxaparin for prophylaxis of venous thromboembolism in patients with acute ischaemic stroke. Furthermore, the significant reduction in the incidence of venous thromboembolism also indicated a significant reduction in proximal deep vein thrombosis with enoxaparin compared with unfractionated heparin. This result has important clinical implications as there is a strong predictive correlation between proximal deep vein thrombosis and the risk of symptomatic venous thromboembolism.[29]

A limitation of our study was its open-label design. An open-label study is subject to bias in the declaration of potential endpoints. In PREVAIL, the primary efficacy endpoint of venous thromboembolism was composed largely of asymptomatic events that were assessed systematically. Neurological worsening, which included an increase in the NIHSS score of 4 or more points, triggered assessment of possible symptomatic intracranial haemorrhages. All endpoints were adjudicated by a central, blinded adjudication committee. Furthermore, as in many other similar studies, symptomatic deep vein thrombosis and pulmonary embolism events might have been under-reported, especially in this high-risk population of patients who probably have confounding diagnoses.

Enoxaparin is preferable to unfractionated heparin for venous thromboembolism prophylaxis in this high-risk medically ill patient population in view of its better clinical benefits to risk ratio and convenience of once daily administration.

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Contributors

All authors participated in the study design, collection of data, interpretation of results, and writing and critically reviewing or revising the report. All authors have seen and approved the final version of the report, and were fully responsible for content and editorial decisions.

Conflict of interest statement

All authors were members of the PREVAIL study steering committee. DS has received honoraria from Sanofi-Aventis for speaker bureau and consultancy. CK has received honoraria for membership of speaker bureaus for Boehringer-Ingelheim and Sanofi-Aventis, and from Organon for consultancy. WO'R was a principal investigator at a study site for both PREVAIL and EXCLAIM studies (sponsored by Sanofi-Aventis). GP has received honoraria from Sanofi-Aventis, Pfizer, BMS, and Leo for consultancy. GA has been a member of scientific advisory boards and a principal investigator in clinical trials funded by AstraZeneca, Sanofi-Aventis, Novartis, and Boehringer Ingelheim.

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Protective efficacy of a monovalent oral type 1 poliovirus vaccine: a case-control study

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See Articles page 1363

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Summary

Background **A high-potency monovalent oral type 1 poliovirus vaccine (mOPV1) was developed in 2005 to tackle persistent poliovirus transmission in the last remaining infected countries. Our aim was to assess the efficacy of this vaccine in India.**

Methods **We estimated the efficacy of mOPV1 used in supplementary immunisation activities from 2076 matched case-control pairs of confirmed cases of poliomyelitis caused by type 1 wild poliovirus and cases of non-polio acute flaccid paralysis in India. The effect of the introduction of mOPV1 on population immunity was calculated on the basis of estimates of vaccination coverage from data for non-polio acute flaccid paralysis.**

Findings **In areas of persistent poliovirus transmission in Uttar Pradesh, the protective efficacy of mOPV1 was estimated to be 30% (95% CI 19–41) per dose against type 1 paralytic disease, compared with 11% (7–14) for the trivalent oral vaccine. 76–82% of children aged 0–23 months were estimated to be protected by vaccination against type 1 poliovirus at the end of 2006, compared with 59% at the end of 2004, before the introduction of mOPV1.**

Interpretation **Under conditions where the efficacy of live-attenuated oral poliovirus vaccines is compromised by a high prevalence of diarrhoea and other infections, a dose of high-potency mOPV1 is almost three times more effective against type 1 poliomyelitis disease than is trivalent vaccine. Achieving high coverage with this new vaccine in areas of persistent poliovirus transmission should substantially improve the probability of rapidly eliminating transmission of the disease.**

Introduction

By early 2004, the transmission of indigenous wild poliovirus had been interrupted in all but six countries of the world as a result of a concerted international eradication effort.[1] In four of these countries—Nigeria, Niger, Pakistan, and Afghanistan—sustained transmission was the result of a failure to immunise a sufficiently high proportion of children against poliomyelitis.[2] However, In India and Egypt, poliovirus transmission persisted despite immunisation coverage with four doses of the trivalent oral poliovirus vaccine of more than 90% among children aged less than 5 years.[3,4]

In recognition of the grave threat that persistent transmission in India and Egypt posed to the Global Polio Eradication Initiative, the programme's international oversight body urgently reviewed a range of options in October, 2004, to enhance the effectiveness of vaccination in these areas. By that time, transmission of wild type 2 poliovirus had been interrupted worldwide and type 3 poliovirus had been eliminated in Egypt and all but one state of India. Consequently, the Advisory Committee on Polio Eradication recommended the rapid development, licensing, and introduction of a new monovalent oral type 1 poliovirus vaccine (mOPV1).[1] This new vaccine possesses five times the potency of licensed monovalent vaccines used in the early 1960s (1×10^6 median cell culture infective doses [$CCID_{50}$] *vs* 200 000 $CCID_{50}$ per dose).[5] Through an extraordinary public-private development effort this new mOPV1 was licensed by April, 2005, in India and Egypt and used in mass polio immunisation campaigns in India (April, 2005) and Egypt (June, 2005).[6,7]

The efficacy of mOPV1 has major implications for international public health. The Global Polio Eradication Initiative has invested US$5 billion in eradication over a 20-year period and a key role is now proposed for monovalent vaccines in the strategic approach to interrupting the transmission of remaining indigenous wild poliovirus and managing the risks of re-emergent transmission of poliovirus after global certification of eradication.[8,9]

Especially important to the programme is the effectiveness of the monovalent vaccine under field conditions of poor sanitation and high population density, where a high prevalence of diarrhoeal disease and other infections have been shown to interfere with the efficacy of trivalent oral poliovirus vaccine as well as to favour the transmission of wild poliovirus.[10–12] In Egypt, no indigenous strain of wild poliovirus has been detected since the introduction of mOPV1.[6] In India, however, a polio outbreak in 2006 allowed us to study the efficacy of this new vaccine under field conditions. Our aim was to determine the protective efficacy of mOPV1 in India and explore the consequent implications of mOPV1 for global polio eradication and post-eradication risk management.

Methods

Patients and procedures

Since the introduction of mOPV1 use in India in 2005, vaccination efforts have focused on the northern states of

Uttar Pradesh—where over 80% of all type 1 cases of poliomyelitis in India in 2006 occurred—and Bihar. Frequent rounds of vaccination with mOPV1 have been interspersed with use of trivalent vaccine to maintain immunity to type 3 poliovirus. In the few districts with continued reporting of type 3 poliomyelitis, monovalent vaccine against type 3 (mOPV3) has also been used in up to two immunisation rounds.

We extracted data for cases of type 1 poliomyelitis and control individuals from the database of the National Polio Surveillance Project, which detects and investigates cases of acute flaccid paralysis in children aged less than 15 years in India. The National Polio Surveillance Project is an active surveillance system that receives reports from over 10 000 health-care institutions and 15 000 health-care practitioners.[13] All cases of acute flaccid paralysis undergo standard clinical, epidemiological, and laboratory investigations, including the collection of two stool samples to test for wild poliovirus. Data were extracted for patients in whom paralysis developed between January 1, 1997, and December 31, 2006. Laboratory confirmation of suspected cases of poliomyelitis was not routinely done before this time. Cases of acute flaccid paralysis without information on vaccine doses received or that did not have two adequate stool samples and had residual paralysis compatible with poliomyelitis were excluded from the analysis.

Institutional ethics approval was not sought since this is not a prospective intervention study. The paper reports an analysis of a National Surveillance database recording use of standard vaccines licensed by the National Regulatory Authority of the Government of India for use in India. The database is anonymised and free of personally identifiable information.

A case of type 1 poliomyelitis was defined as any case of acute flaccid paralysis with virological confirmation of type 1 wild poliovirus. Virological confirmation was done by the national laboratory network supported by the National Polio Surveillance Project. We estimated the sensitivity of laboratory testing for type 1 poliovirus from the consistency in results across the two stool samples collected from each case of acute flaccid paralysis.[14] The tests are assumed to be 100% specific since virus is grown in culture and all positive samples are sequenced in the VP1 region of the viral genome to allow differentiation of genotype and to identify any identical sequences that would indicate potential cross-contamination of samples.

Cases of acute flaccid paralysis from which wild poliovirus was not isolated from stool samples were defined as non-polio acute flaccid paralysis and could have been caused by a wide range of conditions including Guillain-Barré syndrome, trauma, and infection with other enteroviruses.[15] Control individuals were selected from these cases of non-polio acute flaccid paralysis and were matched to each case of poliomyelitis by district, age of onset of paralysis (to within 1 month), and date of onset of paralysis (to within 3 months). Matching criteria were chosen to reduce differences in exposure to wild poliovirus between cases and controls to a minimum, and are consistent with criteria used previously to estimate the efficacy of the trivalent vaccine.[10] We estimated the probability that a case of non-polio acute flaccid paralysis was actually infected with type 1 poliovirus (ie, the risk of misclassification) from the sensitivity and specificity of laboratory testing and the prevalence of type 1 poliovirus among all reported cases of acute flaccid paralysis.[14]

The number of doses of oral poliovirus vaccine reported by the parent to have been received by each case and control was extracted from the case investigation data. Individuals who recorded dose information were masked to the polio status of the child, which only became available after virological testing of the stool samples. These data do not differentiate between doses of oral poliovirus vaccine received through routine immunisation services, which use only trivalent vaccine, and supplementary immunisation activities, which use trivalent or monovalent vaccine. We therefore estimated the efficacy of mOPV1 under the assumptions of either 0% or 100% coverage by routine services. In the first case, we assumed that none of the total reported doses of vaccine were received through routine services. In the second case, the first three doses reported by cases and controls were assumed to have been trivalent vaccine received through routine services. The number of doses of monovalent and trivalent vaccine received by each case and control through supplementary immunisation activities was determined from their exposure to activities with different vaccine types based on their district of residence, date of birth, and date of onset of paralysis. For example, a child born on November 22, 2004, in Moradabad district in Uttar Pradesh, with date of onset of paralysis of November 12, 2005, would have been exposed to seven rounds of supplementary immunisation, four of which were with mOPV1 and the rest with trivalent vaccine. To estimate the number of doses of oral poliovirus vaccine of a particular type received by a child with acute flaccid paralysis, we multiplied the number of doses reported to have been received by the child by the fraction of supplementary immunisation activities that used vaccine of that type.

Statistical analysis

Vaccine efficacy was calculated by comparing the number of doses received by cases with that of matched controls by use of conditional logistic regression.[16] The odds of infection with paralytic poliovirus in India shows a log-linear relationship with the number of doses of trivalent vaccine received.[10] This finding is consistent with the mechanism of action of oral poliovirus vaccine, which shows an all-or-nothing response to vaccination in terms of protection against paralytic disease, with a probability of protection per dose that is independent of the number

	Cases of poliomyelitis	Matched cases of poliomyelitis
Age (years)		
<1	1820 (37%)	851 (41%)
1–2	2471 (50%)	1051 (51%)
3–4	458 (9%)	141 (7%)
5+	217 (4%)	33 (2%)
Location		
Uttar Pradesh	2973 (60%)	1499 (72%)
Bihar	439 (9%)	204 (10%)
Rest of India	1554 (31%)	373 (18%)
Period		
1997–2001	2540 (51%)	816 (39%)
2002–2006	2426 (49%)	1260 (61%)
Exposed to mOPV1, assuming		
(a) no routine tOPV	534 (11%)	451 (22%)
(b) first three doses routine tOPV	479 (10%)	405 (20%)
Total	4966 (100%)	2076 (100%)

Data are n (%). mOPV1=monovalent oral type 1 poliovirus vaccine. tOPV=trivalent oral poliovirus vaccine.

Table 1: **Characteristics of matched cases of type 1 poliomyelitis and all reported cases of type 1 poliomyelitis, 1997–2006**

of earlier doses.[17,18] We therefore estimated the log-odds of a paralytic infection with type 1 poliovirus as a linear function of the number of doses of vaccine of different types:

$$\ln(\text{odds}) = \beta_m x_m + \beta_t x_t + E$$

See Online for webappendix

where $(1-e^{\beta_m})$ is the per-dose protective efficacy of mOPV1 against type 1 paralytic poliovirus, $(1-e^{\beta_t})$is the per-dose protective efficacy of the trivalent vaccine against type 1 poliovirus, and x_m and x_t are the number of doses of mOPV1 and trivalent vaccine received, respectively. Each matched case-control pair has a particular level of exposure to wild poliovirus, E, which is unknown and can be eliminated from the analysis by maximising the conditional likelihood.[16] We estimated vaccine efficacy separately for the states of Uttar Pradesh and Bihar, and for the rest of India, by including an interaction term, since the efficacy of trivalent vaccine in these two northern states has been shown to be lower than in the rest of India.[10] We also examined the possibility of interference between mOPV1 and doses of trivalent vaccine by testing for an interaction.

To examine the hypothesis of a constant efficacy per dose for mOPV1, we also treated the estimated number of doses received as a categorical variable, and this unconstrained model was compared with the model with a constant per dose efficacy by use of the likelihood ratio statistic. Potential differences in mOPV1 efficacy by age were also examined by the inclusion of an interaction term for the age at onset of paralysis by 6-month age-groups. We tested the robustness of the process used to assign the vaccine type of each reported dose by examining the estimated efficacy of oral poliovirus vaccine irrespective of vaccine type before and after the introduction of monovalent vaccine in 2005.

The overall effectiveness of mOPV1 in Uttar Pradesh was assessed by calculating the proportion of children who were protected by vaccination against type 1 paralytic poliovirus, by 3-month age-groups, in the last quarter of 2004 (ie, just before the introduction of mOPV1) and the last quarter of 2006. This was estimated from the number doses of mOPV1 and trivalent vaccine received by children with non-polio acute flaccid paralysis, who are assumed to have the same level of vaccine coverage as other children from the same age-group and location, and the estimated efficacy for each of these vaccines (see webappendix for further details). A comparison was made with the estimated proportion of children protected in the last quarter of 2004 in the rest of India, where wild poliovirus transmission had been interrupted for the previous 2 years and continued immunisation had maintained the reproductive number below one, the threshold for persistence.[10] Immunity among 0–23-month-old children in the rest of India at this time is therefore indicative of exposure to vaccine virus alone, not wild poliovirus. The implications of mOPV1 for post-eradication risk management were assessed by calculating the number of doses of mOPV1 or of trivalent vaccine required to achieve a level of protection comparable with that which interrupted wild poliovirus transmission and maintained polio-free status in the rest of India.

All statistical analyses were implemented with the statistical programming language R.

	Vaccine	Location	Vaccine efficacy
	Trivalent	Rest of India	23% (17–29)
		Bihar	19% (8–29)
		Uttar Pradesh	11% (7–14)
No routine tOPV	Monovalent	Rest of India	36% (0–72)
		Bihar	18% (0–43)
		Uttar Pradesh	30% (19–39)*
First three doses routine tOPV	Monovalent	Rest of India	42% (0–71)
		Bihar	19% (0–47)
		Uttar Pradesh	31% (20–41)†

Data are efficacy (95% CI). tOPV=trivalent oral poliovirus vaccine. *Significantly better than trivalent vaccine in Uttar Pradesh, p=0·0007. †Significantly better than trivalent vaccine in Uttar Pradesh, p=0·0004.

Table 2: **Estimated per dose protective efficacy of mOPV1 and trivalent vaccine against paralysis by type 1 poliovirus in India**

Role of the funding source

The funding source had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data. NCG had final responsibility to submit for publication.

Results

122 173 cases of acute flaccid paralysis were identified. Of these, 2580 did not have two adequate stool samples and had residual paralysis compatible with poliomyelitis and were thus excluded from the analysis; a further 5773 cases did not report the number of vaccine doses received and were also excluded. 4966 cases of type 1 poliomyelitis had complete dose information for the entire study period; of these, 2076 were matched with suitable controls (table 1). The age distribution of matched cases was much the same as that for all reported cases of poliomyelitis. There was a greater probability of finding a matched control in Uttar Pradesh in recent years because there were more reported cases of non-polio acute flaccid paralysis in this region compared with other parts of India; in 2006, 388 (86%) cases of type 1 poliomyelitis reported from Uttar Pradesh were matched with a control. Between 438 and 460 matched controls were exposed to at least one supplementary immunisation activity with mOPV1, depending on the assumed routine coverage with trivalent vaccine.

We estimate that the protective efficacy of mOPV1 in Uttar Pradesh is 30% (95% CI 19–39) per dose under the assumption of no routine coverage with trivalent vaccine and 31% (20–41) under the assumption of 100% coverage of routine programmes with up to three doses of trivalent vaccine (table 2). Both efficacy estimates are significantly higher than that for trivalent vaccine against type 1 poliovirus in Uttar Pradesh, which we estimated to be 11% per dose, irrespective of the assumption about routine coverage ($p=0·0007$ and $0·0004$ for each assumption). The estimate of mOPV1 efficacy is largely independent of the assumption about routine coverage with trivalent vaccine. Therefore, our (conservative) point estimate of mOPV1 efficacy is 30% per dose, with a CI of 19–41%, which spans the intervals for our two estimates. In Bihar and the rest of India, there were insufficient cases of poliomyelitis in 2006 to allow us to estimate mOPV1 efficacy precisely (table 2). As expected, there was no significant interaction between doses of mOPV1 and of trivalent vaccine in protecting against paralytic type 1 poliovirus, since supplementary immunisation activities occured at least 4 weeks apart to avoid interference between vaccine virus doses ($p=0·54$ and $p=0·21$ for each assumption).

The estimated odds of infection with paralytic poliovirus was found to fall exponentially with increasing number of doses of mOPV1 or trivalent vaccine, consistent with the assumption of a constant vaccine efficacy per dose (webfigure 1). Furthermore, the model with a constant probability of providing protection per dose did not give a significantly worse fit than the unconstrained model with differing efficacy by number of vaccine doses previously received (likelihood ratio test $p=0·9$). The estimated efficacy of mOPV1 was not dependent on age at onset of paralysis.

We estimated that the sensitivity of testing for type 1 poliovirus from cases of acute flaccid paralysis with two stool samples was 97%, which is consistent with previous estimates.[10,19] The prevalence of type 1 poliovirus among all cases of acute flaccid paralysis was estimated to be 4·7% and the probability of misclassifying a child paralysed by type 1 poliovirus as a non-polio acute flaccid paralysis control to be 0·0017.

Figure 1 shows the effect of mOPV1 on the proportion of children protected by vaccination against type 1 paralytic poliovirus for Uttar Pradesh, assuming 0% routine coverage with trivalent vaccine. Similar results were found when we assumed that there was 100% routine coverage with trivalent vaccine (webfigure 2). The number of doses of oral poliovirus vaccine received by children aged 0–23 months, as estimated from data

See Online for webfigures 1 and 2

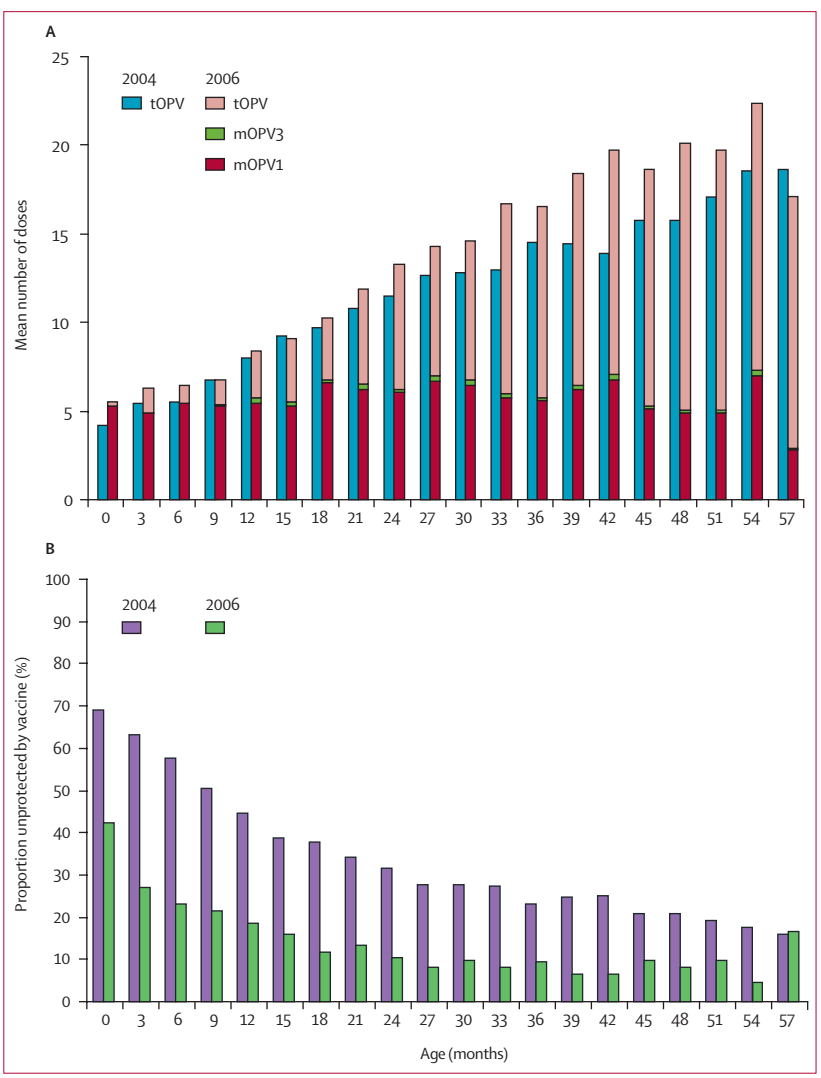

Figure 1: **The effect of monovalent vaccine on population immunity among children in Uttar Pradesh**
Calculations assume that all doses were received through supplementary immunisation campaigns. (A) The mean number of doses of each type of oral poliovirus vaccine received by children in Uttar Pradesh by 3-month age-groups, comparing the last quarter of 2004 with 2006. (B) The proportion of children in Uttar Pradesh who remained unprotected by oral vaccine against type 1 paralytic poliovirus in the last quarter of 2004 and 2006, based on the estimated coverage and efficacy of monovalent and trivalent vaccines. mOPV1=monovalent oral type 1 poliovirus vaccine. mOPV3=monovalent oral type 3 poliovirus vaccine. tOPV=trivalent oral poliovirus vaccine.

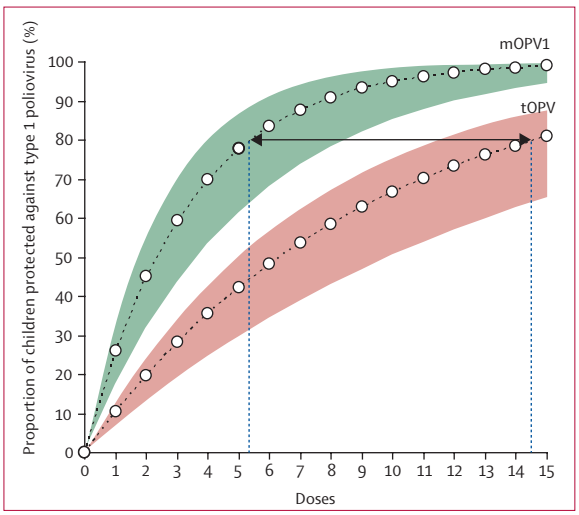

Figure 2: **Proportion of children protected against type 1 paralytic poliovirus**
Based on vaccine efficacy estimates for Uttar Pradesh. The shaded areas represent 95% CI for the per dose efficacy estimates. mOPV1=monovalent oral type 1 poliovirus vaccine. tOPV=trivalent oral poliovirus vaccine.

for cases of non-polio acute flaccid paralysis, shows a marginal improvement, from an average of seven doses in the last quarter of 2004 to eight doses for the same period in 2006 (figure 1). However, there was a substantial improvement in population immunity between the two periods, since in 2006 about half of the doses received in this age-group were mOPV1 (45–69%, depending on assumed coverage of routine services; figure 1 and webfigure 2). Consequently, in the last quarter of 2004, 59% of children aged 0–23 months in Uttar Pradesh were protected against type 1 poliovirus, compared with 76–82% of children in this age-group in the last quarter of 2006. This finding is comparable with an estimated 81% of children aged 0–23 months protected against type 1 poliovirus in the rest of India (excluding Bihar) during the last quarter of 2004.

The overall protective efficacy of vaccine given to children in Uttar Pradesh, irrespective of the inferred vaccine type, was estimated to be 25% (95% CI 17–31) per dose in 2006, compared with 9% (5–14) in the 5 years preceding the distribution of monovalent vaccine ($p=0·0002$). This increase in overall vaccine efficacy following the introduction of mOPV1 supports the notion that this vaccine has greater efficacy than does trivalent vaccine, irrespective of the process used to classify the type of vaccine for each reported dose.

The greater efficacy of mOPV1 leads to much more rapid protection of children than with trivalent vaccine in Uttar Pradesh (figure 2). Each child would need to receive about five doses of mOPV1 to achieve an estimated 78% (range 61–87) level of vaccine-generated immunity, which is comparable with that needed to interrupt wild poliovirus transmission in the rest of India. By contrast, 14 doses of trivalent vaccine would be needed to reach such a level of protection.

Discussion

Our results show that, in the state of Uttar Pradesh, the monovalent vaccine is about three times more likely to result in a protective immune response against type 1 paralytic poliomyelitis than is the trivalent vaccine, irrespective of the assumption about routine immunisation. This increased efficacy is probably caused by the absence of interference between the three Sabin vaccine strains.[20] Even balanced formulations of trivalent poliovirus vaccines tend to result in preferential infection and seroconversion to type 2 virus, especially in developing countries, most likely explaining the global eradication of wild type 2 poliovirus in 1999.

The relative efficacy of mOPV1 is somewhat better than expected from seroconversion studies after vaccine administration, in which a relative rate of seroconversion per dose of 2–2·5 was found.[5] However, an estimated per dose efficacy of 30% is substantially lower than an overall seroconversion rate of 72% (range 53–89) observed in four small studies from developing countries,[5] which is probably the result of the higher prevalence of diarrhoea and other infections in Uttar Pradesh. Such infections can severely compromise the efficacy of live-attenuated oral poliovirus vaccine, as has been shown for the trivalent vaccine.[11,12] Vaccine quality is unlikely to be a problem, since temperature-sensitive vaccine vial monitors have been used in India since 1998, and routine testing of samples of vaccine vials from the field have found consistently high vaccine potency (>10^6 $CCID_{50}$ per dose). We were unable to generate precise estimates of the efficacy of mOPV1 outside Uttar Pradesh; nevertheless, efficacy is probably higher in the rest of India because of the lower prevalence of diarrhoea and other infections.

Although the estimated per dose efficacy of mOPV1 is below that observed in other studies, its efficacy was three times greater than that of the trivalent vaccine in the same setting, which has important implications for interrupting the remaining chains of wild poliovirus transmission in India as well as managing post-eradication risks. Most importantly, our estimate that 76–82% of children aged 0–23 months were protected by vaccine against type 1 paralytic poliovirus in Uttar Pradesh in the last quarter of 2006 due to the use of mOPV1 in over half the supplementary immunisation activities compares favourably with the estimated 81% achieved in the rest of India (excluding Bihar) at the end of 2004 when endemic transmission of type 1 wild poliovirus had been stopped for 2 years and the reproductive number maintained below the threshold for persistence.[10] In both cases, actual population immunity will be somewhat higher than these estimates of primary vaccine-derived immunity, due to natural exposure to wild poliovirus, secondary vaccine virus transmission, and the presence of maternal antibodies that protect children in the first few months of life.

Although a proportion of the children who seroconvert after immunisation with oral poliovirus vaccine can still

become infected with poliovirus, the observation of a herd effect sufficient to interrupt transmission in the rest of India is consistent with studies that show that the duration and titre of viral excretion in children who become infected after immunisation are substantially reduced compared with unimmunised children.[21–23] In Uttar Pradesh, the proportion of children that need to be protected to interrupt transmission could be higher than in the rest of India, since higher population densities and poorer sanitation probably result in a greater transmission potential of wild poliovirus.

The higher per dose efficacy of mOPV1 compared with trivalent vaccine would facilitate a much more rapid increase in population immunity during an outbreak response in the post-eradication era. In the setting of Uttar Pradesh, five doses of mOPV1 would be needed to protect about 80% of children against type 1 poliomyelitis (figure 2). A comparable level of protection with trivalent vaccine would require 14 doses. This lends support to the idea of the stockpiling monovalent vaccines for managing the risks associated with polioviruses in the post-eradication era, as proposed by the Advisory Committee on Polio Eradication.[6]

Several factors could affect the precision of our estimate of the field efficacy of mOPV1. The number of doses of vaccine of different types recorded for each case of acute flaccid paralysis relies on accurate reporting of doses received and correct classification of the vaccine dose administered. Any misreporting that might have occurred is unlikely to have affected our estimate of vaccine efficacy, since more detailed follow-up of a subset of cases of poliomyelitis in 2005 found no tendency towards under-reporting or over-reporting of doses. Misclassification of vaccine doses received by individuals with acute flaccid paralysis will lead to an underestimate of the true mOPV1 efficacy, since trivalent doses could erroneously be recorded as mOPV1. Although such a misclassification could have some effect on our estimate of mOPV1 efficacy, the proportion of children missed by each supplementary immunisation activity is small (<5%) and exposure to different types of such activities is strongly correlated with the number of doses reported by individuals with acute flaccid paralysis, suggesting misclassification—and misreporting—is limited (webfigure 3). That mOPV1 is more effective than trivalent vaccine is lent strong support by the increased estimated efficacy of oral poliovirus vaccine in 2006, irrespective of vaccine type, compared with the 5 years before its introduction. Before the introduction of mOPV1, estimated vaccine efficacy based on data gathered since 1997 did not change over time.[10]

Children with non-polio acute flaccid paralysis are a suitable control group for the analysis since they come from the same communities as reported cases of poliomyelitis. The estimate of vaccine efficacy would be biased if these children were in fact paralysed due to infection with type 1 poliovirus. However, the estimated probability of misclassification is very low; indeed, just three cases of type 1 poliomyelitis would be expected to be misclassified as controls over the entire period of the analysis and less than one during 2005–06, when mOPV1 was in use. Although just under half the cases of type 1 poliomyelitis could be matched, the tendency to select recent cases from Uttar Pradesh in the analysis of efficacy does not introduce bias, since the analysis is stratified by location and there has been no temporal change in the efficacy of the trivalent vaccine.[10] Furthermore, the estimate of mOPV1 efficacy is largely based on matched case-controls from the outbreak in 2006 centred on Uttar Pradesh, when 86% of cases were matched with controls. Indeed the estimated efficacy of mOPV1 remains at 30% per dose (range 19–41) when based on these cases alone.

Further studies are required to refine our understanding of the field efficacy of mOPV1, and also monovalent vaccine against type 3 poliovirus, and their role in interrupting the final chains of wild poliovirus transmission worldwide and managing post-eradication risks. Seroconversion studies after administration of trivalent vaccine and mOPV1 should be completed in India and elsewhere to assess the relative immunogenicity of these vaccines in different settings. However, most important to the elimination of poliovirus from the four remaining endemic areas in the world is achieving and sustaining high coverage with oral poliovirus vaccine of the appropriate type in all geographical areas and among all population subgroups. The 2006 outbreak of type 1 poliomyelitis in India, despite the introduction of a substantially more efficacious vaccine since mid-2005, serves as stark evidence of the need for high coverage with multiple doses of vaccine as early as possible in life in these areas. Achieving such coverage will require sustained dialogue with local communities and strong political commitment. If these conditions can be met, the prospects are now very good for the elimination of wild poliovirus transmission worldwide.

Contributors

NCG and RBA conceived the analysis and wrote the final manuscript, NCG applied the analysis, JW coordinated surveillance of acute flaccid paralysis, SD supported the analysis, SB supervised data collection, JMD did the laboratory testing of cases, and DLH and RWS contributed to the concept and review of the paper. All authors reviewed the analysis and contributed to the writing of the paper.

Conflict of interest statement

We declare that we have no conflict of interest.

See Online for webfigure 3

Acknowledgments

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Eradication versus control for poliomyelitis: an economic analysis

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Summary

Background Worldwide eradication of wild polioviruses is likely to yield substantial health and financial benefits, provided we finish the job. Challenges in the four endemic areas combined with continuing demands for financial resources for eradication have led some to question the goal of eradication and to suggest switching to a policy of control.

Methods We developed a dynamic model, based on modelling of the currently endemic areas in India, to show the importance of maintaining and increasing the immunisation intensity to complete eradication and to illustrate how policies based on perception about high short-term costs or cost-effectiveness ratios without consideration of long-term benefits could undermine any eradication effort. An extended model assesses the economic implications and disease burden of a change in policy from eradication to control.

Findings Our results suggest that the intensity of immunisation must be increased to achieve eradication, and that even small decreases in intensity could lead to large outbreaks. This finding implies the need to pay even higher short-run costs than are currently being spent, which will further exacerbate concerns about continued investment in interventions with high perceived cost-effectiveness ratios. We show that a wavering commitment leads to a failure to eradicate, greater cumulative costs, and a much larger number of cases. We further show that as long as it is technically achievable, eradication offers both lower cumulative costs and cases than control, even with the costs of achieving eradication exceeding several billion dollars more. A low-cost control policy that relies only on routine immunisation for 20 years with discounted costs of more than $3500 million could lead to roughly 200 000 expected paralytic poliomyelitis cases every year in low-income countries, whereas a low-case control policy that keeps the number of cases at about 1500 per year could cost around $10 000 million discounted over the 20 years.

Interpretation Focusing on the large costs for poliomyelitis eradication, without assessing the even larger potential benefits of eradication and the enormous long-term costs of effective control, might inappropriately affect commitments to the goal of eradication, and thus debate should include careful consideration of the options.

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Introduction

Economic assessments have prospectively supported the case for poliomyelitis eradication worldwide.[1–3] While preventing hundreds of thousands of cases of paralytic poliomyelitis and premature deaths, the US domestic poliomyelitis vaccination programme also yielded net economic benefits that exceeded US$180 000 million, even without considering the large, intangible benefits associated with avoided fear and suffering.[4] These US net benefits greatly exceed the cumulative global investment of more than $4000 million (with much more contributed at the national level) over nearly 20 years for the Global Polio Eradication Initiative (GPEI) by external donors.[5] We anticipate that retrospective economic analysis of the GPEI will also show substantial net benefits, if eradication is completed.

In addition to these specific analyses for poliomyelitis, numerous other analyses address the questions and issues related to eradication versus control.[6–13] Notably, Barrett[6] emphasised that a disease could be controlled and eliminated locally, but that eradication requires elimination everywhere at the same time, which requires cooperation. Building on that work, Barrett[7] specifically explores the investment in eradication and finds that "maintaining a very high level of control can never be optimal, given the technical feasibility of eradication." This insight is particularly important because it runs counter to the recent suggestion that control should be maintained such that the "annual global number of cases is less than 500" (ie, a policy of high control in perpetuity).[14] Barrett and Hoel[8] explicitly explore the dynamics of poliomyelitis eradication and provide estimates of thresholds for the welfare cost of paralytic poliomyelitis that must be exceeded to justify eradication (shown separately for rich and poor countries). Geoffard and Philipson[9] showed that private markets might have difficulty achieving eradication when the demand for vaccines depends on the prevalence of disease (ie, the demand for vaccine vanishes when prevalence is low enough), and they explore the incentives of various stakeholders. They also show that, for public health expenditures, if the prevalence inversely affects demand for vaccination (ie, perceived benefit of vaccination drops as prevalence decreases) then this leads to a failure to eradicate.

The GPEI succeeded in reducing yearly cases of paralysis from wild polioviruses from an estimated 350 000 cases in 1988 to about 2000 cases in 2006.[15]

Nonetheless, the goal of worldwide poliomyelitis eradication now faces substantial challenges that include: curtailing transmission of wild polioviruses in the remaining endemic countries; managing the risks of vaccine-derived polioviruses (viruses derived from live oral poliovirus vaccine that have mutated towards neurovirulent forms similar to wild polioviruses); containing live polioviruses in laboratories and vaccine production facilities; and addressing concerns about the risks of reintroductions into countries previously free of wild poliovirus transmission.[16–25]

The emergence of circulating vaccine-derived polioviruses in areas of low vaccine coverage[20,26] provides strong motivation for either maintaining high coverage or completely stopping vaccination with oral poliovirus vaccine in the future.[24,27,28] However, the most important challenge is to justify the continued use of resources (both financial and human) to complete eradication in the next few years. Concerns about whether poliomyelitis eradication is realistic and that "international assistance for polio could have negative effects on other public health efforts" has led to the suggestion that "the time has come for the global strategy for polio to be shifted from 'eradication' to 'effective control.'"[14] This recommendation represents a radical shift in policy not supported by estimates of the financial or health implications, and we believe that policymakers should consider any policy change in the context of information about the future risks, costs, and benefits of the alternative options.

Wild polioviruses could theoretically be eliminated in all parts of the world.[29] In practice, the GPEI has successfully used existing vaccines to eradicate type 2 wild polioviruses worldwide and eliminate type 1 and 3 in all but four countries, in which transmission of these two serotypes has never been disrupted. In these remaining endemic areas the challenges to elimination differ. Vaccination campaigns in India continue to miss a small percentage of young children in a large and high-density population rapidly generating susceptible people, and sub-optimum immune response to the oral vaccine further compounds the challenge.[30–32] In Nigeria, operational and political issues continue to pose problems, not unlike the challenges faced by that country during the Smallpox Eradication Programme.[33] In Afghanistan and Pakistan the challenges relate to security issues associated with current conflicts. Nonetheless, the GPEI overcame similar issues in the past, and accepting these barriers as being insurmountable at this advanced stage should be an unpopular political choice. We emphasise that our analysis focuses on the trade-offs of control versus eradication, assuming that eradication is achievable provided that we are willing to commit the necessary resources, and not on the feasibility of eradication.

In this paper, we develop a dynamic model to show the importance of maintaining and increasing the intensity of immunisation in currently endemic areas to complete eradication. We extend the model to indicate how policies based on perception about high short-term costs or cost-effectiveness ratios without consideration of long-term benefits can undermine any eradication effort and lead to suboptimum policy decisions. Finally, we assess the economic implications and disease burden of a change in policy from eradication to control, and make the case that physicians and global leaders should carefully consider the long-term costs of failing to fully commit to poliomyelitis eradication now.

Methods

We previously developed a model to assess the risks, costs, and benefits of global policies for managing poliomyelitis after eradication[24,34–37] that stratified the world according to 2002 World Bank income levels.[38] This model defined eradication as interruption of wild poliovirus transmission globally. It also included the risks and costs of post-eradication outbreaks from different sources (including vaccine-derived viruses), and recognised the need for high-quality surveillance to ensure that wild polioviruses no longer circulate. In this Article, we modify that model to address the crucial questions related to whether to achieve eradication or switch to a control approach (webappendix). We first simplified and adapted our existing dynamic poliomyelitis outbreak model[35] to explore the long-term effects of reducing vaccination intensity on the incidence (ie, the number of new paralytic cases per year) of paralytic cases due to circulation of an endemic poliovirus. We focused on modelling the epidemiologic block consisting of the populous Indian states of Uttar Pradesh and Bihar, in which endemic transmission continues to pose challenges.[30] The estimated population of these states in 2006 of 274 million people[39] represents around 10% of the entire population of all low-income countries (2002 World Bank income levels).[38] We consider a 20-year time period because control options imply sustained efforts; therefore, we expanded the original outbreak model to include mortality from all causes and waning immunity. We also assumed circulation of only one serotype (with a paralysis to infection ratio of 1:200, consistent with type 1 poliovirus, which accounted for over 85% of wild poliovirus cases between 2002–06).[40–43] We defined the aggregate oral poliovirus immunisation intensity (u) as the fraction of susceptible people who become immune because of exposure to oral vaccine viruses per year (ie, from successful routine or supplemental oral vaccination, or secondary exposure to oral poliovirus vaccine). Using u provides a conceptual representation of the effect of immunisation in the model and eliminates the need to individually estimate routine immunisation coverage, coverage of campaigns by age, vaccine take rates, and secondary oral vaccine rates.[35] The fact that immunisation activities in Uttar Pradesh and Bihar deliver doses to most age cohorts with susceptible people (ie, children younger

than 5 years) at roughly the same rate,[30] motivated us to simplify to a single-age-cohort model. Since Uttar Pradesh and Bihar clearly represent a geographic area in which polioviruses show high transmissibility, we assume an R_0 of 16 (a theoretical measure that represents the average number of secondary infections introduced by one infectious person in a fully susceptible population).[35] Currently, the relatively low incidence of paralytic poliomyelitis in Uttar Pradesh and Bihar compared with its current population size suggests that the average aggregate oral poliovirus vaccine immunisation intensity has been close to the threshold ($\hat{u}$) necessary to eradicate polioviruses from this population.[44] We explore the effects of changes in u on the burden of paralytic cases.

Building on the insights of others,[7–9] we extend the Uttar Pradesh and Bihar model to explore the implications of adding a constraint of tolerable cost-effectiveness ratio (in $ per paralytic case). We implement this extension by use of a decision rule that substantially reduces immunisation intensity (ie, setting u to a value below $\hat{u}$) as soon as the perceived cost-effectiveness ratio reaches the tolerable cost-effectiveness ratio compared with a decision rule that ceases vaccination after the prevalence of infection drops below 1 (ie, eradication). We define the perceived cost-effectiveness ratio as the yearly vaccination costs corresponding to a particular immunisation intensity divided by the perceived yearly incidence of paralytic cases. The perceived incidence equals the true incidence with a 1-year delay, which represents the time taken to recognise changes in incidence and react by changing the immunisation intensity. This model starts at the pre-vaccine equilibrium. For these and subsequent analyses, we report costs in US$ (2002) and discount costs and cases over time using a 3% rate following standard methods.[45]

To extend the insights obtained from these modelling efforts to a broader region and the larger debate about eradication versus control, we explored the meaning of control compared with eradication for the group of

	Routine vaccination	SIA rounds per year	Surveillance	Response	Population immunity	
					At outset	Heterogeneity*
Theoretical control scenarios (shown in figure 5A)						
No control	None	None	Passive	No response	NA	NA
Very low control	OPV	None	Passive	No response	NA	NA
Very high control†	OPV	Two	AFP‡	Very aggressive‡	NA	NA
Extreme control§	IPV	None	AFP	NA	NA	NA
Modelled control scenarios (shown in figure 5B)¶						
0	OPV	None	Passive	No response	Realistic	None
1	OPV	None	Passive	2 x tOPV, delay 180 days	Realistic	None
2	OPV	None	AFP	2 x tOPV, delay 180 days	Realistic	None
3	OPV	None	Passive	3 x mOPV, delay 120 days	Realistic	None
4	OPV	None	AFP	3 x mOPV, delay 120 days	Realistic	None
5	OPV	Two in three years ||	Passive	No response	Maximum	High
6	OPV	Two in three years ||	Passive	2 x tOPV, delay 180 days	Maximum	High
7	OPV	Two in three years ||	Passive	3 x mOPV, delay 120 days	Maximum	High
8	OPV	One	Passive	No response**	Maximum	Medium
9	OPV	Two ||	Passive	No response††	Maximum	Low
Post-eradication options (shown in figure 5B)						
No routine	None	None	Passive	3 x mOPV, delay 45 days	Realistic	None
IPV	IPV	None	Passive	3 x mOPV, delay 45 days	Realistic	None
OPV	OPV	None	Passive	3 x mOPV, delay 45 days	Realistic	None
OPV +SIAs	OPV	1‡‡	Passive	3 x mOPV, delay 45 days	Maximum	Medium

SIA=supplemental immunisation activity. OPV=oral poliovirus vaccine. AFP=acute flaccid paralysis. IPV=inactivated poliovirus vaccine. tOPV=trivalent oral poliovirus vaccine. mOPV=monovalent oral poliovirus vaccine. *Column indicates different distributions for the probability of population immunity reduction from the income group average population immunity for a given importation outbreak. With the distribution noted as probability (no reduction, 2-fold increase in proportion effective susceptible, 3-fold increase in proportion effective susceptible), the different reduction levels are: none=probability (1, 0, 0); low=probability (0·9, 0·1, 0); medium=probability (0·75, 0·25, 0·05); and high=probability (0·6, 0·3, 0·1). †Option includes costs of two yearly SIAs in all non-endemic low-income countries and six yearly SIAs in endemic areas. ‡Surveillance and response costs included in $280 million annual costs of maintaining A in the endemic areas. §This extreme scenario includes costs for a universal campaign with two doses of IPV attaining 100% coverage among all people (including adults) to ensure immunity for all individuals at the outset in addition to 100% coverage with three inactivated poliovirus vaccine doses throughout the 20-year time horizon. ¶Assuming effective control that costs $280 million per year to maintain A=1300 cases in endemic areas per year (see webappendix for effect of reductions in the goal for endemic cases A), plus the costs and cases associated with the strategies in non-endemic areas listed here. ||Assuming the two rounds occur in a paired fashion at a 30-day interval. **Assuming the next single tOPV SIA round starts 180 days after virus introduction. ††Assuming next two tOPV SIA rounds start 165 days after virus introduction. ‡‡For post-eradication scenarios, we modelled the number of rounds probabilistically to account for uncertainty in the future frequency using a triangular distribution with a mean close to 1.

Table: **Scenarios and key assumptions**

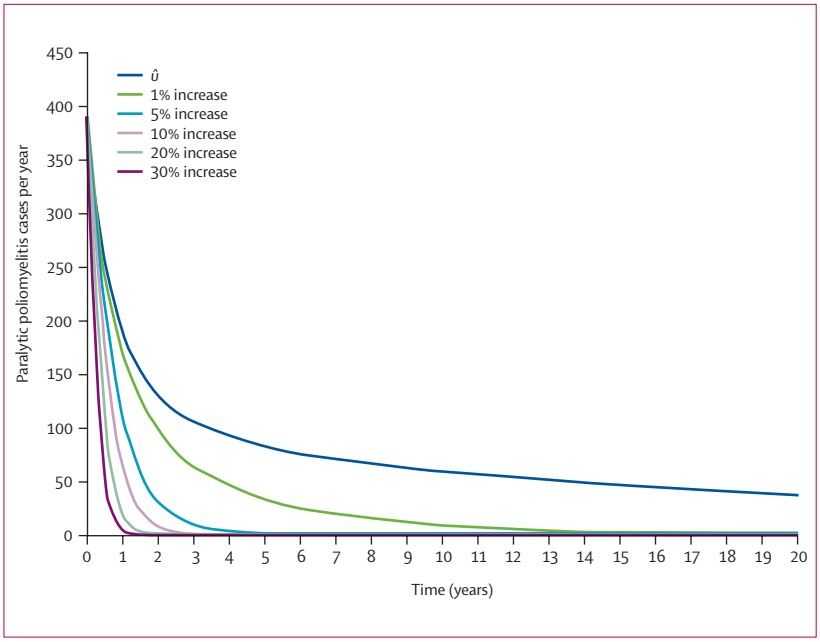

Figure 1: **Paralytic poliomyelitis cases per year in the Indian states of Uttar Pradesh and Bihar with the fraction of susceptible people that become immune due to exposure to oral poliovirus vaccine virus per year (u) equal to or greater than the threshold ($\hat{u}$) needed for eventual eradication**

low-income countries. Our previous modelling identified these countries as likely to have the greatest future burden of cases, but we emphasise that the costs and cases for these countries underestimate the full global values since they omit middle-income and high-income countries. Additionally, although we assume a 20-year time horizon, the decisions made now will affect many future generations.

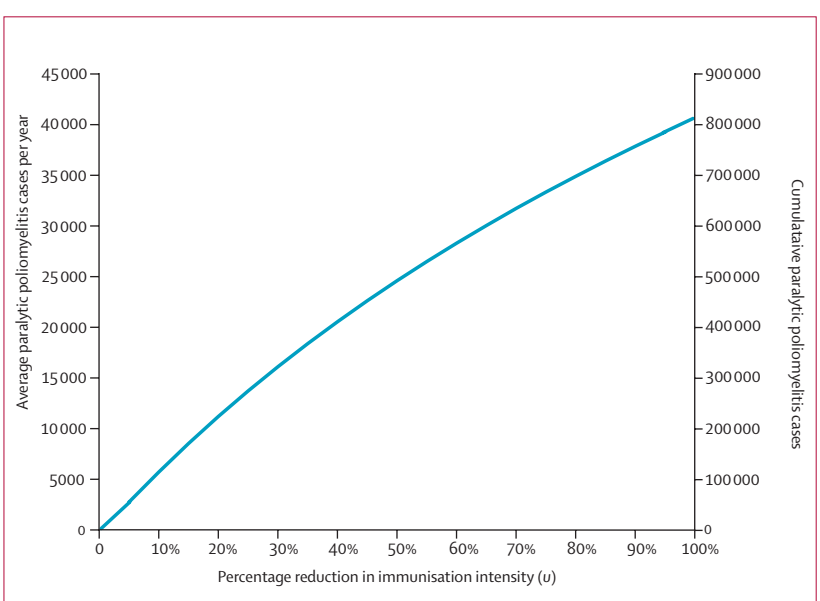

Figure 2: **Paralytic poliomyelitis cases (undiscounted) over a 20-year time horizon in the Indian states of Uttar Pradesh and Bihar for different reductions of u away from the threshold ($\hat{u}$) needed for eventual eradication**

To account for the possibility of future resurgence of wild poliovirus in our model, which otherwise started with successful eradication, we added the risk of outbreaks into countries previously free of wild poliovirus transmission, based on the frequency of such outbreaks between 2000–06.[15,46] We partitioned the low-income group into the currently endemic areas (ie, Afghanistan, Nigeria, Pakistan, and Uttar Pradesh and Bihar, about 25% of the low-income population) and the remaining non-endemic areas in the low-income group. We model the average conditions and risks in the low-income group and included more heterogeneity (eg, age groups and outbreak-specific population immunity and R_0s), to estimate the expected number of paralytic cases in the non-endemic areas as a result of wild polioviruses importations and outbreaks of circulating vaccine-derived poliovirus. We optimistically assume that the control policy involves sufficient resource allocation similar to the current expenditures in endemic areas to maintain the number of endemic cases at an acceptable level, A. Although we did not extrapolate from the Uttar Pradesh and Bihar model for the base case results, we analysed the effect of assuming lower expenditures in the endemic areas based on the Uttar Pradesh and Bihar model.

A range of control scenarios is summarised in the table. At the extremes, we note four theoretical control scenarios of academic interest: (1) no control, which implies the maximum number of cases and paying no costs (including paying no treatment costs); (2) very low control, which implies abandoning the GPEI, relying solely on routine immunisation, with no system or external funding for outbreak response or acute flaccid paralysis surveillance, and paying treatment costs; (3) very high control, which maintains A cases of wild polioviruses per year at the cost needed to achieve this; and (4) extreme control, which assumes use of inactivated poliovirus vaccine with 100% coverage and implies maximum costs but theoretically minimum cases,[47] although it is implausible to achieve now. We suggest that the combinations of costs and cases associated with these theoretical bounds provide insights into the possible trade-offs between costs and cases. For the very low control scenario, we assume that the accumulation of susceptible people and neglect of endemic areas will lead to widespread transmission of wild polioviruses in low-income countries, with 1 in 200 susceptible people, mainly infants and children, contracting paralytic poliomyelitis. For this scenario, we directly estimate the number of susceptible people based on vaccine take rates,[35] projected coverage,[48] and projected birth rates.[49] For the very high control scenario, we include costs of $280 million for two rounds of supplemental immunisation activities per year in all non-endemic low-income countries and six rounds of supplemental immunisation activities per year in endemic areas. These costs are consistent with the recent expenditures of the GPEI that kept endemic cases

to an average of around 1300 per year during the past 5 years,[15] which implies for this scenario that A=1300.[15] With respect to more realistic modelled control scenarios (table), we characterise a range of possible control scenarios for the non-endemic areas, and added to these the costs and cases associated with very high control that keeps endemic cases at A.

We assume that during the next few years the current high intensity of supplemental immunisation activities, aggressive outbreak control, and robust surveillance of acute flaccid paralysis will continue, and thus the time horizon begins at the point when cases drop to A, which might imply additional costs and time to get from the current incidence to any lower A (eg, fewer than 500 cases as has been suggested by others[14]). The eradication options begin with complete interruption of poliovirus transmission and include four future vaccination policies for the post-eradication world (ie, no routine immunisation, routine oral poliovirus vaccination with supplemental immunisation activities, routine oral poliovirus vaccination without supplemental immunisation activities, or routine inactivated poliovirus vaccination). We do not include any additional costs of eradication for these options so that we can explore the amounts that we should be willing to pay to finish eradication when comparing these options to the control options. The total number of paralytic poliomyelitis cases includes wild poliovirus cases in endemic areas as well as importations into areas previously free of wild poliovirus transmission for each control scenario, cases of vaccine-associated paralytic poliomyelitis for any scenarios that use routine oral poliovirus vaccine, supplemental immunisation activities, or outbreak response, and cases from outbreaks of circulating vaccine-derived poliovirus for all scenarios.

Results

Based on modelling the recent experience in northern India, we show the effects of changing the intensity of immunisation (u) with respect to paralytic incidence. Figure 1 shows that u must be increased to achieve eradication and that the relative amount of increase determines the time until eradication. Even small reductions of u from the immunisation intensity required for eventual eradication $\hat{u}$ could lead to rapid accumulation of susceptible people and result in many paralytic cases (figure 2). For example, a reduction of only 10% in u leads to more than 110 000 cumulative paralytic cases over 20 years (ie, more than 5000 cases per year on average), and a reduction by 50% leads to around 500 000 cases. The greater the reduction away from $\hat{u}$, the larger the oscillations toward a new equilibrium, with the possibility of a large outbreak in the second or third year following the change in u (figure 3). These results suggest that greater intensity of effort will be needed, which in the short-run will increase the perception of high costs and cost-effectiveness ratios.

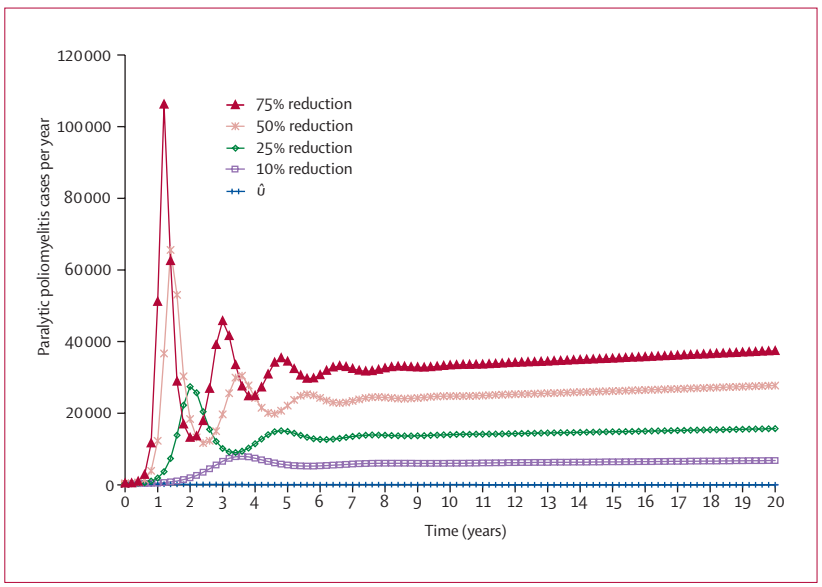

Figure 3: **The incidence of paralytic cases per year in the Indian states of Uttar Pradesh and Bihar with u equal to or less than the threshold ($\hat{u}$) needed for eventual eradication**

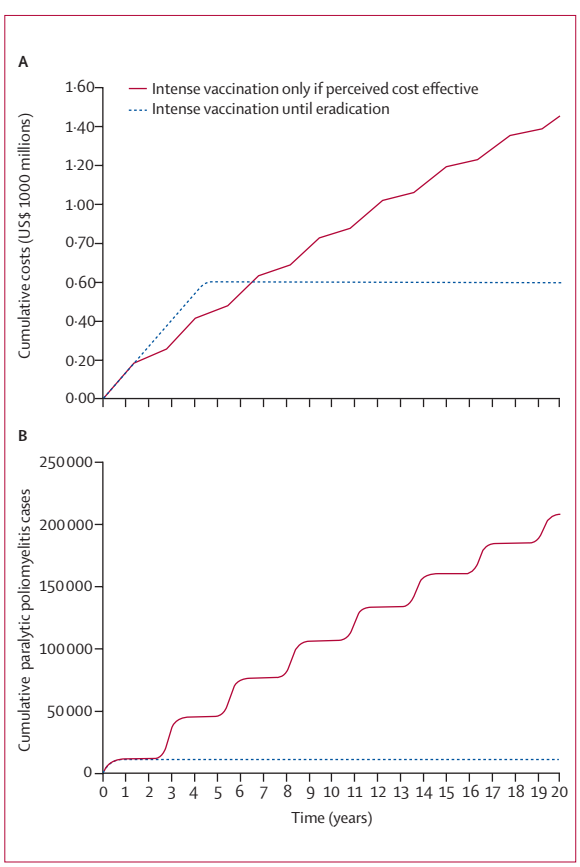

Figure 4: **Cumulative costs and cases in Uttar Pradesh and Bihar for a strategy of pursuing eradication versus intense vaccination only while the perceived cost-effectiveness ratio (PCER, $ per case) remains below the tolerable cost-effectiveness ratio (TCER, $ per case)**
(A) Cumulative costs. (B) Cumulative paralytic cases.

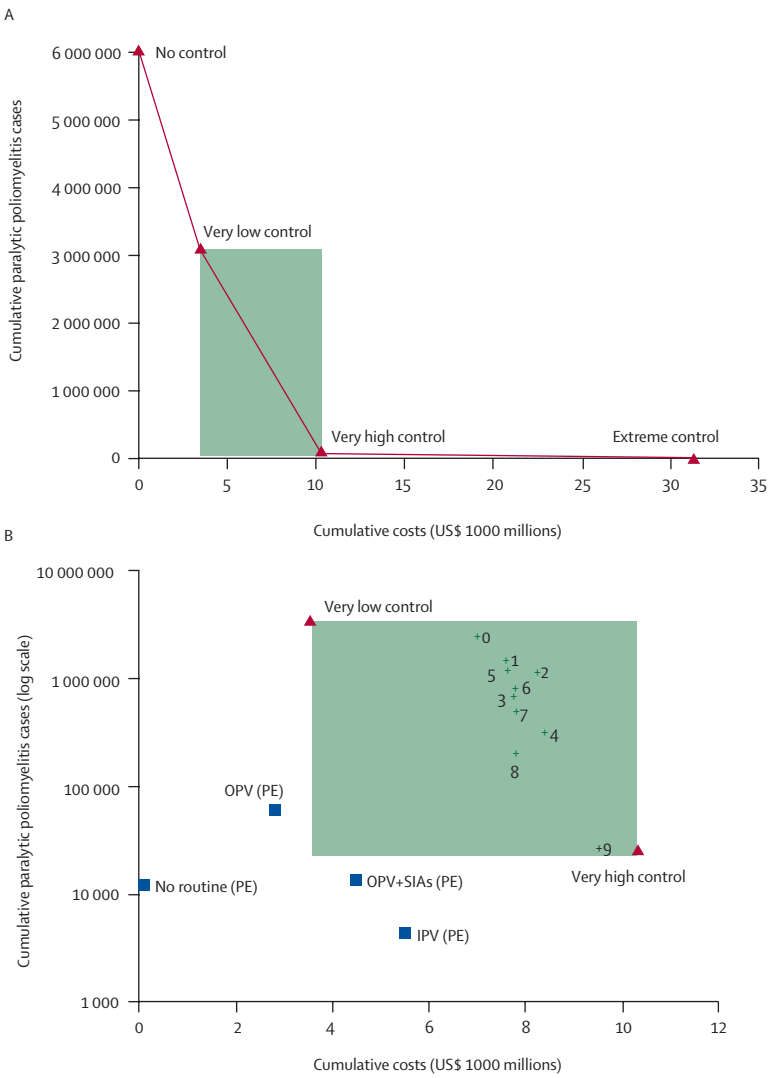

Figure 5: **Expected costs and cases of various scenarios for low-income countries, discounted over a 20-year time horizon**

(A) Theoretical control scenarios (linear scale). (B) Realistic options with cases on a logarithmic scale. See table for assumptions for each point. Financial costs do not include societal willingness-to-pay for prevented paralytic cases. IPV=inactivated poliovirus vaccine. OPV=oral poliovirus vaccine. PE=post-eradication. SIAs=supplemental immunisation activities.

Building on the work of Geoffard and Philipson,[9] we show that if demand for vaccination decreases after reaching the tolerable cost-effectiveness ratio, then the disease will never be eradicated, with cycles of demand resulting from delays in perceived incidence or other delays. Once the perceived cost-effectiveness ratio is higher than the tolerable cost-effectiveness ratio, vaccination will decrease, costs will come down, and with some delay cases will rise. The delay with which cases rise depends on the reduction in immunisation intensity, consistent with figure 3. We note a steep increase in cases because they accumulate rapidly between the time of the outbreak and the delayed recognition that a higher level of control is again cost effective (ie, that the perceived cost-effectiveness ratio is less than the tolerable cost-effectiveness ratio). Figure 4 shows that the cumulative costs and cases initially grow at a similar rate, but thereafter the strategy that pursues eradication incurs greater costs in the relatively short-term for marginal reductions in cases. However, several years after eradication (ie, sometime during year 6 with the assumptions used in this example), the cumulative costs for the two strategies become equal, and thereafter the control strategy costs more (figure 4A). This situation occurs because in the longer-term, the eradication strategy no longer accumulates substantial costs. By contrast, the control strategy that keeps the cost-effectiveness below the tolerable cost-effectiveness ratio continues to require resources (although fewer resources during periods when vaccination is not perceived as cost effective). These results show that a wavering commitment (in this case due to perceived high costs or cost-effectiveness ratios) leads to a failure to eradicate and to greater cumulative costs and much larger numbers of cases (figure 4B).

Figure 5 shows the expected discounted financial costs and cases for the various scenarios that we considered for control versus eradication for low-income countries. Adding the treatment costs to the no control option makes it more expensive than the low control option, and thus we emphasise that the theoretical bound of no control is not an ethical or feasible option (figure 5A). Similarly, the theoretical extreme control scenario is currently impossible because sufficient inactivated poliovirus vaccine capacity does not presently exist, and low-income countries do not have the necessary infrastructure to approach 100% coverage (even high-income countries do not attain 100% coverage). The option of eradication followed by continued use of oral poliovirus vaccine without supplemental immunisation activities represents an undesirable option because it leads to on-going outbreaks of circulating vaccine-derived polioviruses and cases of vaccine-associated paralytic poliomyelitis at relatively high costs. The option of eradication followed by no routine vaccination represents the lowest cost option and also leads to fewer expected cases than the oral poliovirus vaccine options (figure 5B). Because of the risks associated with outbreaks of circulating vaccine-derived polioviruses after cessation of oral poliovirus vaccine, the model yields different non-zero numbers of expected cases depending on whether cessation of oral poliovirus vaccine is followed by inactivated poliovirus vaccine with projected routine coverage or no routine immunisation, which means that the risks of reintroduction of live polioviruses will require active management into the future.

Although we would ideally like to know the optimum case-cost frontier for the control options (ie, the lowest

number of cases achievable for a given investment of costs in control), the actual kinetics are uncertain, and will depend on the assumptions. Nonetheless, we find that the realistic control scenarios all imply costs and cases that far exceed the eradication options despite assuming the challenging objective of actually controlling transmission to keep the number of endemic cases below *A*. Low cost options (ie, implying low control) will lie in the region to the right and slightly below the very low control theoretical bound.

The control scenario with no supplemental immunisation activities and no outbreak response (labelled with a 0 in figure 5B) is the model equivalent of the theoretical very low control scenario, except that it assumes higher costs in the endemic areas to keep endemic cases below *A* and thus falls below and to the right of the theoretical bound. On the other end of the scale, the control scenario with two rounds of supplemental immunisation activities per year and no outbreak response (labelled with a 9 in figure 5B) lies above the corresponding theoretical bound of very high control, because some possibility exists of circulating vaccine-derived polioviruses or outbreaks of wild poliovirus in the non-endemic areas even with frequent supplemental immunisation activities, while both assume *A* cases per year in the endemic areas at the same cost. The difference in costs stems from a different assumption about surveillance in the non-endemic areas (table 1). Increasing *A* moves the control options left and up, which translates into lower cost but more cases. The very low control scenario yields a total of more than 3 million discounted cases over the 20-year time horizon, or about 200 000 cases per year.

Finally, we can also assess the difference in the net benefits of a selected eradication option (eg, no routine immunisation after eradication) and the best possible control option as a function of the societal willingness to pay to prevent a case, and view the difference as the amount that we should be willing to spend to achieve eradication. This analysis implies that for a willingness to pay of $5300 per paralytic poliomyelitis case, we should be willing to invest more than $8000 million to achieve eradication based on analysis of low-income countries alone and a 20-year time horizon.

Discussion

Our analysis of low-income countries suggests that eradication is always a better option than control, and that we should be willing to pay thousands of millions of dollars more to achieve this goal. Although we intentionally focused most of our analysis on the low-income countries because they will incur most of the burden of cases if eradication fails, all nations will continue to incur financial costs, implying that the true global willingness to pay is even higher. By contrast, for any low-control scenario we will probably see a disease burden approaching the implied equilibrium number seen in 1988 of 350 000 cases for a worldwide population of 5000 million people.[49] Although the rate with which the number of cases would increase would depend on how quickly the percentage of the population immune to disease declines, our results suggest that low control would ultimately lead to a world with many hundreds of thousands of children paralysed every year (ie, approaching the theoretical bound of very low control), while still needing a sustained financial investment in poliovirus vaccination and treatment. We characterised numerous options for high control, and we note that they all lead to very high costs, which would be difficult to sustain in view of the challenges that exist in closing the financial gaps for eradication now. The GPEI faces financial challenges in the face of large potential savings of both costs and cases. The world is unlikely to support high control in the absence of these potential savings. Thus, our results suggest a very strong economic and public health case for completing poliovirus eradication now.

We believe that focusing on the large costs for poliomyelitis eradication in the absence of estimates of the even larger potential benefits of eradication and the enormous long-term costs of effective control might inappropriately affect commitments to the goal of eradication. This concern is particularly important in view of the reality of constraints on financial resources, many competing opportunities for resources, and the cognitive challenges that arise in considering stocks and flows.[50] Short-term thinking often prevails. As a result we are overly affected by the state of the world now, we fail to adequately account for the state of the world that will follow, and we misunderstand how much the choices we make now will determine our future options and opportunites.[51] In the context of poliomyelitis eradication, we only face the choice of eradicating now because the global investment thus far has produced enough immune people to make worldwide simultaneous elimination of wild polioviruses possible. Thus, the investment in eradication led to high levels of population immunity that might not be fully recognised by many people.[50,51] Assuming that we could later simply pay the same financial amount to finish the job represents a cognitive fallacy.[51]

Our analysis suggests that we either complete eradication now, or pay much more (and risk that we might not have another chance) to try to do so later, while continuing to cumulate both costs and cases. Although economic models suggest that when eradication is desirable it should happen instantly,[8] we acknowledge the real and important social, logistical, and managerial challenges that exist and we emphasise that they could unfortunately lead to a failure to achieve the optimum outcome of eradication when combined with concerns about current high costs or cost-effectiveness. Our results suggest that stakeholders in the debate about whether to give up or pursue the current option to eradicate the poliovirus should make

their assumptions about costs and cases of specific options explicit and transparent.

Experience has shown that any circulation of wild polioviruses will lead to outbreaks, even at a time when global population immunity is at its highest. In 2002–03, the GPEI scaled back its immunisation campaigns because of limited financial resources. Political challenges to vaccination in northern Nigeria and coverage gaps in India led to large outbreaks. These conditions led to exportation and a resurgence of wild poliovirus cases in countries previously free of wild poliovirus transmission and necessitated additional expenses exceeding $400 million between 2004–06 to again stop virus circulation in these countries.[27]

As the debate about control versus eradication unfolds, we also note that comparing the eradication of poliomyelitis to other diseases requires caution. For example, comparisons to the one disease that has been eradicated, smallpox, should recognise the very different points in time that eradication began with respect to the stage of control of these diseases. Edward Jenner proposed the idea of smallpox eradication in 1801, and by the time the WHO Intensified Smallpox Eradication Programme began, smallpox had been eliminated in all but 31 countries, with less than 1000 million people living in endemic countries.[52] By contrast, poliomyelitis vaccines became available in the 1950s, and when the GPEI launched in 1988, poliomyelitis was endemic in 125 countries with 90% (roughly 4500 million people) living in endemic countries. Thus, any comparisons of the costs of these two eradication efforts should clearly account for differences in the magnitudes of the burdens at the beginning, in addition to the increased size of the population and value of money. Moreover, smallpox eradication involved only one virus serotype, whereas eradication of wild polioviruses requires the interruption of transmission of three serotypes.

Eradication will depend on people in endemic countries overcoming the barriers that currently exist. In northern India, our analysis suggests that such efforts will need an even greater intensity of immunisation. Although many countries would like to stop oral poliovirus vaccination now, maintaining the highest rate of population immunity is of crucial importance until at least the last case. National leaders will need to continue to appreciate the very large long-term benefits of eradication as they pay high short-term costs to intensify immunisation and deal with the reality of some stakeholder perceptions that low incidence of disease should mean less investment of resources.

The decision to change course from eradication to control represents a costly option that does not consider the longer-term implications. Although eradication is expensive, our work and previous studies show the fallacies of failing to sustain the commitment. Oral poliovirus vaccination has already produced benefits in the USA that far exceed the worldwide costs of eradication.[4] We find that the continued commitment and substantial investment in finishing the job of global eradication represents a much more attractive option than an indefinite policy of control, both in economic and in public-health terms. Therefore, the opportunity costs of a control policy remain far larger than that of an eradication policy, but this requires explicit consideration of the cost and cases of the options.

Contributors

K M Thompson and R J Duintjer Tebbens developed the model, did all of the modelling and analysis, and wrote and edited the manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

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Treating excessive sweating with poison

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A 23-year-old woman presented with hyperhidrosis localised to her right forearm and the back of her right hand. She had experienced hyperhidrotic attacks since childhood. They had become more frequent and troublesome over the years, and now occurred on average five times a day, lasting about 30 min. The excessive sweating was embarrassing for our patient; her hand literally dripped with sweat, affecting her work. Attacks occurred spontaneously or were precipitated by emotional stress, exercise, alcohol, or coffee. The skin was of otherwise unremarkable appearance. The patient had no other symptoms and was otherwise healthy. Treatment with topical aluminium chloride and tap-water iontophoresis over the previous 2 years had not provided relief. A skin biopsy specimen showed increased numbers of eccrine sweat glands without any other abnormality, consistent with an eccrine naevus (figure). The problem resolved following intradermal injections of botulinum toxin, as confirmed by repeated Minor's iodine-starch tests over a period of 6 months. The treatment was well tolerated and the patient's quality of life appreciably improved. In recent years, botulinum toxin has been used as a therapeutic option for hyperhidrosis. These photographs illustrate the profound effects of botulinum toxin injections in focal hyperhidrosis caused by an eccrine naevus.

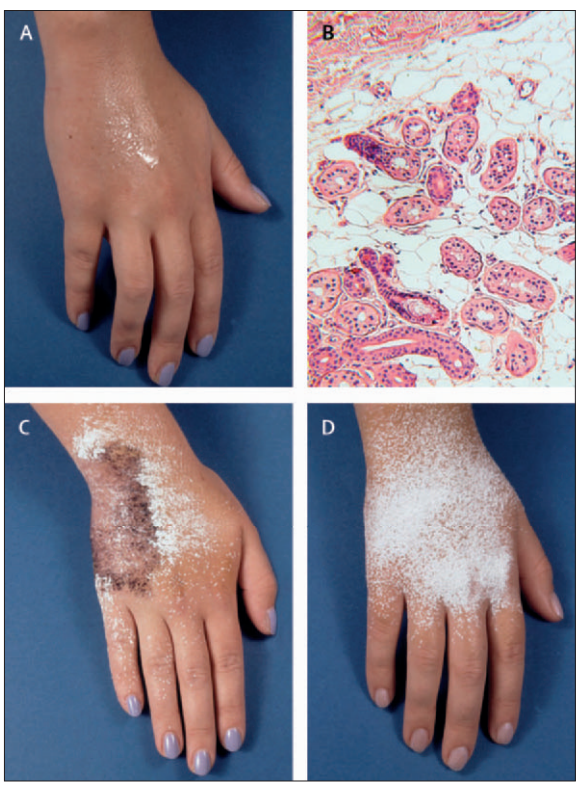

Figure: **Hyperhidrosis and its resolution**
(A) The patient's hand during an episode of hyperhidrosis. (B) Histology showing increased numbers of eccrine sweat glands (haematoxylin and eosin staining). Magnification ×60. (C) Area of excessive sweating visualised by Minor's iodine-starch test. (D) Efficacy of botulinum toxin injections visualised by Minor's iodine-starch test.

Oslo Ministerial Declaration—global health: a pressing foreign policy issue of our time

*Ministers of Foreign Affairs of Brazil, France, Indonesia, Norway, Senegal, South Africa, and Thailand**

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Under their initiative on Global Health and Foreign Policy, launched in September, 2006, in New York, the Ministers of Foreign Affairs of Brazil, France, Indonesia, Norway, Senegal, South Africa, and Thailand issued the following statement in Oslo on March 20, 2007—In today's era of globalisation and interdependence there is an urgent need to broaden the scope of foreign policy. Together, we face a number of pressing challenges that require concerted responses and collaborative efforts. We must encourage new ideas, seek and develop new partnerships and mechanisms, and create new paradigms of cooperation. We believe that health is one of the most important, yet still broadly neglected, long-term foreign policy issues of our time. Life and health are our most precious assets. There is a growing awareness that investment in health is fundamental to economic growth and development. It is generally acknowledged that threats to health may compromise a country's stability and security. We believe that health as a foreign policy issue needs a stronger strategic focus on the international agenda. We have therefore agreed to make impact on health a point of departure and a defining lens that each of our countries will use to examine key elements of foreign policy and development strategies, and to engage in a dialogue on how to deal with policy options from this perspective. As Ministers of Foreign Affairs, we will work to: increase awareness of our common vulnerability in the face of health threats by bringing health issues more strongly into the arenas of foreign policy discussions and decisions, in order to strengthen our commitment to concerted action at the global level; build bilateral, regional and multilateral cooperation for global health security by strengthening the case for collaboration and brokering broad agreement, accountability, and action; reinforce health as a key element in strategies for development and for fighting poverty, in order to reach the Millennium Development Goals; ensure that a higher priority is given to health in dealing with trade issues and in conforming to the Doha principles, affirming the right of each country to make full use of TRIPS flexibilities in order to ensure universal access to medicines; strengthen the place of health measures in conflict and crisis management and in reconstruction efforts. For this purpose, we have prepared a first set of actionable steps for raising the priority of health in foreign policy in an Agenda for Action. We pledge to pursue these issues in our respective regional settings and in relevant international bodies. We invite Ministers of Foreign Affairs from all regions to join us in further exploring ways and means to achieve our objectives.

Foreign policy taking up the challenges of global health: a background note

Why this initiative?

At the invitation of the Norwegian Foreign Minister Jonas Gahr Støre and his French colleague Foreign Minister Philippe Douste-Blazy, foreign ministers from Brazil, Indonesia, Senegal, South Africa, and Thailand formed the Global Health and Foreign Policy Initiative in September, 2006.

Globalisation is rapidly changing the perception of foreign policy and international relations. New actors are gaining influence, and the speed of communication and growing interdependence is giving rise to new relationships, networks, and alliances. These factors are creating new opportunities and new challenges.

The Initiative will build the case for why global health should hold a strategic place on the international agenda. It will do this in two ways: by exploring how foreign ministers and foreign policy could add value to health issues of international importance, and by showing how a health focus could harness the benefits of globalisation, strengthen diplomacy and respond to new thinking on human security.

In its work to date, the initiative has outlined the broad linkages between global health and foreign policy and identified a set of basic premises and shared values to guide its work. Using this linkage as a foundation, ten priority areas were chosen in which a stronger, more direct involvement of foreign policy could make a tangible contribution to protecting and promoting health, as well as offer new scope for foreign policy. In Oslo on March 20, 2007, the seven ministers agreed to an ambitious and progressive agenda for action that details its future work in each of the priority areas.

Health matters in foreign policy

During the late 19th and early 20th centuries, health and foreign policy were linked by quarantine restrictions to prevent the spread of disease from country to country. International agreements were designed to help avoid the consequences of trade disruptions. The early 21st century, however, has seen an unprecedented convergence of global health and foreign policy. Health is deeply interconnected with the environment, trade, economic growth, social development, national security, and human rights and dignity. In a globalised and interdependent world, the state of global health has a profound impact on all nations—developed and developing. Ensuring public health on a global scale is of benefit to all countries. Powerful synergies arise when national interest coincides with the need for concerted regional and global action.

While national security focuses on the defence of the state from external attack, national health security relates to defence against internal and external public-health

risks and threats. These are risks and threats that by their very nature do not respect borders, as people, animals, and goods travel around the world faster than ever before. The responsibility of protecting against health threats must therefore be based on the shared commitment and the capacity of countries. Global health security is only as strong as its weakest link.

It is well recognised that health is a fundamental right of every human being and that health is a key element of any strategy aimed at promoting development and combating poverty. Poverty and hunger are major causes of ill health. Health is a main component of the Millennium Development Goals (MDGs), which point to the interconnectedness of the structural causes of poverty and under-development.

But the relevance of foreign policy to global health is not only about national health security on the one hand and development and the MDGs on the other. Foreign policy must engage in health in new ways. For example, health can be a good entry point to initiate dialogue across borders, thus contributing to building trust between parties. In armed conflict there are ten or more civilian deaths for every combat death, but the indirect or excess death toll from war-induced violence, injury, disease, and malnutrition is rarely the subject of political attention.

Armed conflict often leads to the breakdown of health services, with disastrous consequences for people's health and livelihood. Natural disasters cause high casualties, severe damage to health infrastructure, and loss of health workers. Treating the old and new health problems of people who have been internally displaced is virtually impossible. Re-establishing health services should be a primary focus during the reconstruction phase, post-conflict, and in the aftermath of a disaster. Natural disasters generate other challenges for foreign policy including managing the flow of humanitarian aid.

Drivers of change

New technology has transformed communication and access to information. Rapid acceleration of knowledge and discovery in the life sciences, in areas such as genomics, biotechnology, nanotechnology, and so on, means there are new opportunities and new risks to be managed.

The relentless spread of HIV/AIDS in many parts of the world represents a destructive threat to entire societies. Other new and re-emerging infectious diseases (avian influenza, severe acute respiratory disorder, extensively drug-resistant tuberculosis, malaria, poliomyelitis, plague, dengue fever, and so forth) do not respect geographical borders and can be tackled successfully only if nations work together.

The global health arena is unrecognisable from what it looked like even a decade ago. Civil society now represents a major force for change. New partnerships and alliances are emerging that include multiple stakeholders, networks, and movements, within countries and across borders and regions. At the same time there remains space for new structures.

The main actors involved in global health (governments, regional organisations, non-governmental organisations, foundations, private-public partnerships, the World Bank, the International Monetary Fund (IMF), and the UN and its agencies, specifically WHO, UNICEF, UNAIDS, and UNDP) are all influenced by different views, resource flows, principles, objectives and interests—and they are independent from one another. This raises two key governance questions: how will the money be spent and on what? Who will set the global health agenda?

In spite of many positive developments and results, there is evidence of an increase in the social inequalities in health both between and within countries. The Commission on Social Determinants of Health is addressing these issues and is due to report in 2008.

The MDGs have been partly responsible for revitalising interest in global health, and a whole range of activities are being implemented, but progress has been slow. The slow progress has been attributed to broken health systems, the human resources for health crisis, and persisting inequities in access to interventions that could keep people alive and well. If nothing changes, many countries will not attain the health-related MDGs by 2015.

Countries that succeed in meeting the MDGs will experience benefits far beyond the MDGs. The well-functioning health systems that are needed to reduce maternal, newborn, and child mortality and to combat HIV/AIDS, tuberculosis, and malaria will also help countries to cope with other major health concerns such as sexual and reproductive health, newly emerging infectious diseases, accidents and injuries, and chronic non-communicable diseases.

Basic premises and shared values

The work of the initiative is guided by the acknowledgement that globalisation requires new forms of governance in order to ensure sustainable development, social and economic equity, justice, peace, and security. It recognises the need for cooperation and collaboration, a respect for national sovereignty, a sense of shared responsibility, and the attributes of transparency, trust, accountability, and fairness. The initiative is based on the recognition that life is the most fundamental of human rights, and that life and health are the most precious assets. Every country needs a robust and responsive health system (this includes a health workforce, infrastructure, and supplies), a health research system, and a health information system to provide all citizens opportunities to be healthy and to participate fully in the shared responsibilities for global health security.

There are both technical and political dimensions to protecting and promoting global health and human security. This means that health issues do not only belong to ministries of health and the WHO, especially when they are cross-cutting in nature. New mechanisms in addition to the traditional development model are required. Lack of

access to health knowledge and to essential medicines, vaccines, and other products is one of the key factors limiting human development. A focus on people's health and wellbeing must become part of the collective consciousness of policy makers at the highest level, at the national as well as the international level, and within all relevant international bodies. Health-impact assessments of all foreign, trade, and defence policies would do much to advance the cause of health across governments. The road ahead will require alliance building and networking and at times will require difficult political decisions to be taken. Change is needed—a long-term, forward-looking view is required.

Foreign policy taking up the challenges of global health: agenda for action

Adopted by the Ministers of Foreign Affairs of Brazil, France, Indonesia, Norway, Senegal, South Africa, and Thailand in Oslo on March 20, 2007.

In today's era of globalisation and interdependence there is an urgent need to broaden the scope of foreign policy. In our time, the pursuit of pure self-interest of nations might undermine the solutions that respond to the challenges of growing interdependence. We must encourage new ideas, seek and develop new mechanisms for partnerships, and develop new paradigms of cooperation. This new reality creates a need to find shared values that are embodied in the relations between countries.

Protecting the most fundamental opportunity for life for the world's citizens provides both a lens through which to enhance the goals and responsibilities of diplomacy and a call to bring a more active collaboration between foreign ministries, health ministries, and other functions of government around health security issues.

No country can isolate itself from cross-border risks and threats to their national health security. Foreign policy actions in security, trade, conflict and crisis, environment, and human rights have a strong bearing on whether we can achieve national as well as global health security.[1]

Access to basic needs for human survival——water, food, shelter, protection, and freedom from disease—concerns people of all nations. Unless these needs are met, our health and survival are threatened. Food security and health security are common concerns and should be viewed through the same lens. Often a public health threat in one country requires a concerted response that calls for many foreign policy makers to work together. In a very real sense, the development of all nations is a prerequisite to ensure global health security.

The most effective response to global health challenges depends on alliances, cooperation, and partnerships that reflect a respect for national sovereignty and a sense of shared responsibility. They must also be transparent, trustworthy, accountable, and fair. Collaboration can come in all different forms, including South-South, North-North, and South-North cooperation.

Foreign Ministers have identified areas where the kinds of policy positions they adopt can make a significant difference to prospects for global health security. This paper proposes a shared agenda for Foreign Ministers' action. The agenda is organised around three main themes: "Capacity for global health security", "Facing threats to global health security", and "Making globalisation work for all". Each theme identifies specific actions. But the challenges are all inter-linked. Some have a broad cross-cutting impact and respond to a range of challenges, while others are more specific.

Capacity for global health security

1 Preparedness and foreign policy

Preparedness is a cross-cutting theme. For most governments it starts with an emphasis on being ready to respond to health risks and threats to national health security. But increasingly it includes global mechanisms and other measures that enable countries to make an informed and coordinated response. Preparedness is based on a capacity to identify health risks and threats, including those that may be outcomes of the foreign policies practised by individual nations.

Points for collaborative action by foreign ministers:

1.1 Make "impact on health" a point of departure and a defining lens that each of our countries will use to examine key elements of foreign policy and development strategies, and to engage in a dialogue on how to deal with policy options from this perspective. Use all available evidence in the analysis, share the findings, and ensure open access to the analytical process.

1.2 Engage in developing a roadmap for what remains to be done in large-scale disasters and emergencies where foreign ministers have special responsibilities, including the movement of people and equipment across borders. Make use of global instruments such as the International Health Regulations and humanitarian law.

1.3 Support national disaster planning and development of critical national capacity for emergency preparedness, including the capacity to coordinate relief efforts through the development of local relief networks.

1.4 Strengthen the capacity of the UN Secretary General to assume a coordinating role in facilitating actions related to foreign policy in preparedness, planning, and action for global health security. Work in close cooperation with UN Specialized Agencies, Programmes, and Funds.

1.5 Identify critical gaps in capacity for effective implementation of the International Health Regulations with a specific focus on better national and transnational surveillance, outbreak investigation, and disease control.

[1]The concept of "global health security" has yet to be defined. The reference to security should not be understood in terms of threats to the maintenance of peace and security enshrined in the UN Charter. In the context of this initiative global health security is used to mean protection against public health risks and threats that by their very nature do not respect borders. Global health security depends on critical capacity in all countries, combined with a commitment to collaborate, such as spelled out in the International Health Regulations. It is our expectation that a definition for global health security will be agreed at the World Health Assembly.

2 Control of emerging infectious diseases and foreign policy

Efforts should be based on an understanding of the cross-cutting impacts of communicable disease, including pandemic influenza. These efforts must build on a commitment to fairness and mutual trust, such as in sharing information.

Points for collaborative action:

2.1 Commit to the early and full implementation of the International Health Regulations. Call for improved data and accountability mechanisms as well as the rapid scale up of national capacity. Emphasise the need to share information related to any health risk of international importance.

2.2 Exchange experiences and best practices on preventive and emergency response measures toward the outbreak of pandemics.

2.3 Identify gaps in implementation, ensuring the availability of essential medicines, vaccines, and equipment, not only domestically but also within countries that need assistance, including failing states and countries in conflict and crisis.

2.4 Support and facilitate WHO's leadership role and the work of the Global Outbreak Alert and Response Network (GOARN).

2.5 Support the mobilisation of adequate resources for global infectious disease control, including domestic spending, **ODA** spending, and dedicated spending for joint action to improve global health security, through trusted and transparent partnership mechanisms.

ODA
Official development assistance

3 Human resources for health and foreign policy

The current global shortage and maldistribution of trained health workers, particularly nurses, represents a major barrier to preparedness and to national and global health security. The shortage of human resources is influenced by the global economy, incentives for migration, and global negotiation on services. Such influences go beyond the health sector and can only be modified through political action at the national, regional, and global level. At the same time, human resources for health is situated within the broader health development and systems agenda with financing and stewardship issues as key related matters.

Points for collaborative action:

3.1 Support the development of a global framework for tackling the global shortage of health workers, with monitoring and accountability mechanisms, including for tracking recruitment from countries with weak capacity. Facilitate the use of the Diaspora in country of origin and examine the possibility of establishing multilateral and/or bilateral mechanisms that would ensure that the movement of health professionals is mutually beneficial to both sending and receiving countries.

3.2 Encourage the development of national broad plans for human resources for health, including the use of alternative models for care. These should reflect the standards set by the WHO, for use as reference points and drivers of alignment and accountability globally, such as through the Global Health Workforce Alliance (GHWA) and related initiatives.

3.3 Respond to the need to train more health workers and encourage regional and international exchanges at academic institution level as well as the exchange of technical expertise within the Ministries of Health of the region, centres of excellence, and beyond through facilitating strong collaboration and partnerships, including South-South and regional collaboration.

3.4 Support health research, the ethical conduct of research and research capacity building in countries with inadequate capacity. Facilitate better access for researchers from these countries to innovation and to global knowledge networks.

Facing threats to global health security

4 Conflict (pre, during, and post conflict, and as peace is being built)

As part of efforts to promote peace and security, women, children, and men whose lives are under threat must be helped to survive and maintain good health. Lack of access to health services can in itself have a destabilising effect. The need to preserve life and health is a useful starting point for peace building "before logic breaks down" into full conflict. Access cannot be preserved unless health workers and health infrastructure are protected.

Points for collaborative action:

4.1 Recognise that health can be a good entry point to initiate dialogue across borders and to spearhead the resolution of conflict, with the sincere intention of serving the public interest and building trust and legitimacy.

4.2 Recognise the potential in the presence of "global knowledge networks", which cut across borders and are maintained in spite of conflict. They can be building blocks in peace building efforts, but need to maintain their own integrity and independence.

4.3 Support the evolution of a more consistent approach for monitoring suffering in conflict and war. There should be a regular watch on life and health issues and in particular on the indirect consequences of war and conflict on people's health, with a special focus on women as care givers and girls and women threatened by rape and other forms of violence.

4.4 Further develop the case for a health focus in post-conflict reconstruction. This is necessary to set out clearer principles for better health security as a means for re-establishing peace, trust, and legitimacy of government, and to advocate for a strong focus on health issues in the work of the recently established

UN Peace Building Commission, in cooperation with the WHO. Such efforts must respect the basic imperatives and principles that guide a neutral "humanitarian space" reserved for non-state actors.

5 Natural disasters and other crises

Many of the same principles exist for natural disasters and other emergencies as for situations of conflict, but there is not the same early warning and time for "diplomacy". One challenge is to make a neglected crisis visible and not let action be driven by media attention. In a globalised world, there will be a mix of nationals affected by crisis. Foreign ministers and ministries in countries tackling a crisis will be involved in dealing with expatriates that have been affected, as well as dealing with offers of emergency support. Other foreign ministers will be involved in relief efforts and the repatriation of victims.

Points for collaborative action:

5.1 Support the work of the Office for the Coordination of Humanitarian Affairs (OCHA) and the Central Emergency Response Fund (CERF), facilitating early and effective assistance to vulnerable groups in emergencies.

5.2 Ensure that priority is given to restoring a functioning health system (workforce, infrastructure, and supplies) in the aftermath of a crisis.

5.3 Monitor the equitable distribution of aid, specific needs of care givers and marginalised groups, and any shortfalls in the ulfilment of pledges of funding.

6 Response to HIV/AIDS

A high prevalence of HIV infection is not only a threat to personal health, but also to national and global health security, because of the way AIDS undermines human capacity in essential services. The global response to HIV/AIDS has mobilised a dynamic multi-stakeholder, multi-sector movement, with common purpose, inclusive leadership, and linked community and global action.

Points for collaborative action:

6.1 Take up the challenges that HIV/AIDS presents to trade, human rights, peace building, and humanitarian action through a health lens to drive forward a broader agenda for change.

6.2 Commit to the international agreements and political declarations linking and monitoring these commitments, and call for speeding up their implementation. Initiate voluntarily monitoring the actions taken by the countries involved in the Global Health and Foreign Policy Initiative.

6.3 Call for improved and disaggregated data collection on HIV/AIDS in all countries.[2] Raise awareness among diplomats and ambassadors about the impact of HIV/AIDS on economies, institutional capacity, gender, and human rights in order to bring these issues into country-level policy dialogue as appropriate.

7 Health and the environment

Human health and the environment are both outcomes of complex systems that exist in dynamic balance. Given the severity of health threats related to climate change, biosecurity, and biosafety, the linkage between global health and environment should be considered.

Points for collaborative action:

7.1 Make the links between environment policies and global health visible in foreign policy engagements and exploit the synergistic potential of related policy processes.

7.2 Recognise that the potential of biotechnologies to help developing countries achieve the Millennium Development Goals (MDGs) should not be eclipsed by otherwise legitimate security concerns: establish robust governance mechanisms to prevent misuse of the biological sciences, without hindering their positive contribution to development.

7.3 Engage with WHO and the UN Environment Programme on their joint "Health and Environment Linkages Initiative" in order to strengthen the dialogue between governments and civil society in the use of health and environment impact assessments.

7.4 Give further attention to the potentially very severe consequences to health of climate change and support appropriate foreign policy action at relevant regional and global meetings.

Making globalisation work for all

8 Health and development

Health is key to development and combating poverty. Hunger is a major cause of ill health. Structural causes of poverty and hunger are interwoven, and part of a nexus of policies where foreign policies also play an important part. Global partnership for overcoming both structural and economic barriers to development and health is fundamental for reaching the MDGs and reducing vulnerabilities to neglected and emerging infectious diseases.

Points for collaborative action:

8.1 Use the shared interest in global public health as rationale for giving health top priority in the national and international cross-sectoral development agenda. Push for development cooperation models that match domestic commitment and reflect the requirements of those in need and not one that is characterised by charity and donors' national interests.

8.2 Strengthen the efficiency of global health initiatives through improved governance and better co-ordination of multiple, competitive donors and aid providers (UN agencies, international financial

[2] UN High-Level Meeting on HIV and AIDS, New York, June 2, 2006.

G8
Group of Eight nations

institutions, regional mechanisms, **G8**, donor countries, private foundations, together with the coalitions and alliances that bring them together).

8.3 Improve national and regional research capacity and the management capacity of public health systems, taking into account the special needs of the developing countries and using a variety of modalities including twinning, exchange programmes and institutional collaboration, transfer of technology, regional centres of excellence, etc, fostering regional and South-South collaboration based on shared interests.

8.4 Promote modalities and means to enhance the capacity for national and regional production of essential medicines and equipment and for building capacity for national regulation of pharmaceuticals and commodities, quality control, and supply chain management.

8.5 Honour existing financial commitments and initiate innovative financing mechanisms in order to generate additional resources for financing global health investments such as the international drug facility (UNITAID).

8.6 Work together with the IMF and the World Bank to overcome macroeconomic constraints to effective health investment at country level.

9 Trade policies and measures to implement and monitor agreements

International trade policies and agreements need to be placed within the context of protecting and promoting health and wellbeing. A universal, rule-based, open, non-discriminatory, and multilateral trade system, including trade liberalisation, can support global health security, such as enabling the implementation of the International Health Regulations. Ensuring equal and universal access to essential medicines is one example with major relevance for global public health.

[3]Including the WHO regional bodies and secretariats.

Points for collaborative action:

9.1 Affirm the interconnectedness of trade, health, and development, including both trade and health policies in the formulation of all bilateral, regional, and multilateral trade agreements.

9.2 Reaffirm commitment to the Doha Declaration on **TRIPS** and Public Health and foster the full implementation of the TRIPS flexibilities.

TRIPS
Trade-related aspects of intellectual property rights

9.3 Explore the feasibility of a voluntary monitoring mechanism outside **WTO** for the use of TRIPS flexibilities to overcome price and access barriers and examining the implication of other trade agreements, in particular bilateral trade agreements that may limit the use of these flexibilities.

WTO
World Trade Organization

9.4 Encourage WTO members to accelerate national acceptance procedures in order to ensure the entry into force of the amendment of the TRIPS Agreement.

9.5 Explore and leverage multiple and innovative approaches to reduce price and improve access to essential medicines, together with the application of TRIPS flexibilities.

10 Governance for global health security

Improved governance requires review and adaptation to new realities. It could be better achieved through effective national structures, stronger regional collaboration, broader stakeholder participation and clearer contracts and accountability at the international level. In several respects, health offers a platform for exploring the new challenges of governing interdependence. Governance for health is an aspect of deepening global democracy within regional and global institutions. New mechanisms and alliances are increasingly important but need to have their actions better coordinated. Dealing with cross-border issues, such as the vast differences in access to health care, as well as the movement of people, pharmaceuticals, and commodities, represents situation-specific governance challenges and requires attention on a case-by-case basis.

Points for collaborative action:

10.1 Support policies for global health security in the various foreign policy dialogue and action arenas, such as the UN, G8, arenas for economics and trade issues, and within regional and bilateral arenas.

10.2 Establish broader and more coherent national leadership for global health issues, reflecting the interdependency of health and foreign affairs.

10.3 Recognise and affirm the WHO Secretariat and the World Health Assembly as the main arenas for global health governance,[3] with expanded engagement from foreign ministries in the WHA delegations and assistance to the WHO Director General in bringing relevant global health issues into relevant foreign policy arenas.

10.4 Recognise the role of the private sector, knowledge networks, and civil society organisations in the evolution of global public health policy as well as in action that will improve global health security and engage them more effectively in governance, policy dialogue, and implementation of relevant actions.

10.5 Maximise opportunities for joint working to achieve priority health outcomes within regions and across national borders, including a focus on parity of negotiating powers and the building of capacity that is available to all.

10.6 Contribute to financing global health in ways that do not undermine existing commitments to development financing. Continue efforts to conceive of and bring to fruition innovative and sustainable financing mechanisms and their effective use. Initiate a mechanism to track resource flows for international cooperation directed at specific and agreed global health security purposes, particularly the control of infectious and neglected diseases.

Ankylosing spondylitis

Jürgen Braun, Joachim Sieper

Ankylosing spondylitis is a common inflammatory rheumatic disease that affects the axial skeleton, causing characteristic inflammatory back pain, which can lead to structural and functional impairments and a decrease in quality of life. New imaging techniques and therapies have substantially changed the management of this disease in the past decade. Whether inhibition of radiographic progression and structural damage can be reached with available drugs is as yet unclear. Furthermore, treatment with non-steroidal anti-inflammatory agents and physiotherapy remains an important approach to long-term management of patients with ankylosing spondylitis. The new treatment options with tumour necrosis factor blockers seems a breakthrough for patients refractory to conventional treatment.

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Ankylosing spondylitis is the major subtype and a main outcome of an inter-related group of rheumatic diseases now named spondyloarthritides. Clinical features of this group include inflammatory back pain, asymmetrical peripheral oligoarthritis (predominantly of the lower limbs), enthesitis, and specific organ involvement such as anterior uveitis, psoriasis, and chronic inflammatory bowel disease. Aortic root involvement and conduction abnormalities are rare complications of ankylosing spondylitis. Five subgroups are differentiated clinically: ankylosing spondylitis, psoriatic spondyloarthritis, reactive spondyloarthritis, spondyloarthritis associated with inflammatory bowel disease, and undifferentiated spondyloarthritis. The subgroups are genetically linked—the strongest known contributing factor is the MHC class I molecule HLA B27, although others still remain to be identified.

Epidemiology

Ankylosing spondylitis is a disease that affects young people, who generally present at around 26 years of age. Men are more often affected than are women, with a ratio of roughly 2 to 1.[1] About 80% of patients develop the first symptoms at an age younger than 30 years, and less than 5% of patients present at older than 45 years.[1] There is a rough correlation between the prevalence of HLA B27 and the incidence and prevalence of this disease in a specific population.[2] HLA B27 is most prevalent in northern countries and some tribes (with up to 50% of cases), and is highest in Eskimo populations and Haida Indians. Overall, the prevalence of ankylosing spondylitis is between 0·1% and 1·4%, with most of these data coming from Europe. In mid-Europe a prevalence of 0·3–0·5% for ankylosing spondylitis[3,4] and 1–2% for the whole group of spondyloarthritides seems probable, which is similar to that for rheumatoid arthritis.[5] The incidence of ankylosing spondylitis is between 0·5 and 14 per 100 000 people per year in studies from different countries.[6,7] Several factors contribute to these differences. First is the selection of the target populations; second, the selection of screening criteria such as back pain and the choice of diagnostic criteria to confirm the diagnosis; and third, the prevalence of HLA B27 and the distribution of its subtypes, which differs in populations with ethnic background.

Functional restrictions in patients with ankylosing spondylitis and a disease duration of 20 years are greater in those with a history of physically demanding jobs, more comorbid conditions, and in smokers, than in those with higher levels of education and a family history of this disease.[8] Young age at onset of symptoms is associated with worse functional outcomes.[9] In juvenile patients with spondyloarthritides, clinical symptoms can be different and include severe tarsitis.[10] Male patients have more structural changes, including bamboo spine, than do female patients.

Clinical features

Irrespective of the spondyloarthritis subtype, the main clinical features of this group are inflammatory back pain (panel 1) caused by sacroiliitis and inflammation at other locations in the axial skeleton, peripheral arthritis, enthesitis,[11] and anterior uveitis,[12] whereas manifestations in other organs, such as the heart, are rare.[13] Characteristic symptoms of ankylosing spondylitis are spinal stiffness and loss of spinal mobility, which are explained by spinal inflammation, structural damage, or both.[14] Spinal inflammation can arise as spondylitis, spondylodiscitis, or spondylarthritis. Structural changes are mainly caused by osteoproliferation rather than osteodestruction. Syndesmophytes and ankylosis are the most characteristic features of this disease, which are visible on conventional radiographs after some months to many years. Low bone density, osteoporosis,[15] and an increased rate of fractures,[16] which may add to the hyperkyphosis predominantly seen in male patients,[17] add to the burden of disease.

The peripheral arthritis is usually monoarticular or oligoarticular, and affects mainly but not exclusively the lower limbs.[18] The hip and shoulder joints become affect-

Search strategy and selection criteria

The Cochrane Library and Medline were searched from 2000–2006. The search terms "ankylosing spondylitis" and "spondyloarthritis" were used in combination with the terms "epidemiology", "pathogenesis", "genetics", "diagnosis", "management", and "therapy". Publications from the past 6 years were preferentially selected but important ones from the past millennium were also included according to our judgment.

Panel 1: **Modified New York criteria 1984 for ankylosing spondylitis**

Clinical criteria

- Low back pain and stiffness for longer than 3 months, which improve with exercise, but are not relieved by rest
- Restriction of motion of the lumbar spine in both the sagittal and frontal planes
- Restriction of chest expansion relative to normal values correlated for age and sex

Radiological criterion

- Sacroiliitis grade ≥2 bilaterally, or grade 3–4 unilaterally

Definite ankylosing spondylitis is present if the radiological criterion is associated with at least one clinical criterion.[70]

ed in about 20% of patients with this disease. Hip involvement is regarded as a bad prognostic sign,[19] but there is no agreement on the definition of severe disease. Inflammation of entheseal sites takes place not only at classic sites such as the Achilles tendon and the plantar fascia but at many locations, including the spine. Eye inflammation in spondyloarthritides is largely restricted to the uvea and takes place usually unilaterally, but can switch from one side to the other.[12] For reactive spondyloarthritis, the eye can be affected by conjunctivitis.

Skin involvement (psoriasis) and colitis associated with inflammatory bowel disease can be regarded as basic subtype-defining entities with their own genetic background, different from HLA B27, rather than as disease manifestations. However, the spondyloarthritides have also been regarded as one disease with a common genetic background[20] and two major phenotypes.[21]

There are no good studies of prognosis in ankylosing spondylitis. Two retrospective studies[22,23] have suggested that much radiographic progression happens early in the first 10 years of disease, and more recent studies have shown that structural damage at presentation is the best predictor of further damage.[24] Amor and colleagues[19] proposed a list of prognostic items for the whole group of spondyloarthritis including hip involvement and early onset, which has been confirmed.[4]

Pathogenesis

The cause of ankylosing spondylitis and other spondyloarthritides is unknown. The two central features that deserve explanation are inflammation and new bone formation, especially in the spine. Although inflammation is assumed to trigger new bone formation, there is no close correlation between inflammation and osteoproliferation. There is a strong genetic effect in spondyloarthritides, especially in ankylosing spondylitis. About a third of this effect is explained by HLA B27; the remainder, as yet largely undefined, is associated with genes in and outside the MHC.[25] 90–95% of patients with ankylosing spondylitis are positive for HLA B27,[26] and the risk of this disease developing is as high as about 5% in HLA B27-positive individuals, and substantially higher in HLA B27-positive relatives of patients.[27] However, most HLA B27-positive individuals remain healthy.

The possible interaction between bacteria and HLA B27 has a crucial role in models of the pathogenesis of spondyloarthritides. The fact that reactive arthritis is triggered by genitourinary infections with *Chlamydia trachomatis* or by enteritis caused by gram-negative enterobacteria, such as *Shigella*, *Salmonella*, *Yersinia*, and *Campylobacter* spp[28] provides a solid background for this approach, but the evidence for triggering infections in other spondyloarthritides is marginal. The presence of microbial antigens in the synovium of patients with reactive arthritis[29] has suggested that persistence of microbial antigens could be essential for continuing joint inflammation. About 10–20% of HLA B27-positive patients with reactive arthritis develop the full clinical picture of ankylosing spondylitis after 10–20 years.[30] A possibly central role of bacteria in the pathogenesis of spondyloarthritides is further supported by the relation between Crohn's disease, HLA B27 positivity, and ankylosing spondylitis: 54% of HLA B27-positive patients with Crohn's disease develop ankylosing spondylitis, but only 2·6% of HLA B27-negative patients develop this disease.[31] Leakage of the gut mucosa, a result of inflammation caused by colitis such as found in Crohn's disease, leads to an interaction of the immune system with gut bacteria. In about 50% of patients with ankylosing spondylitis but no known Crohn's disease, macroscopic or microscopic mucosal chronic lesions resembling Crohn's disease have been detected in the gut mucosa.[32]

Finally, some evidence of the importance of the B27-bacteria interaction comes from work in animals. HLA B27 transgenic rats develop spondyloarthritis-like features, but many transgene copies are needed to transfer disease. Environmental factors also have a role since HLA B27 transgenic rats bred in a germ-free environment do not develop disease,[33] and gut flora contribute to the colitis.[34] However, persistence of microbial antigens in human spondyloarthritis in typically associated locations seems unlikely, and no candidate bacteria were detected by PCR in biopsies from sacroiliac joints.[35]

Cartilagenous structures—collagen type II and proteoglycan—have been studied as probable targets of an autoimmune response in ankylosing spondylitis.[11,36–39] Although the collagen-II-induced arthritis model resembles rheumatoid arthritis, animals immunised with proteoglycan show features typical of ankylosing spondylitis.[40] In patients with this disease, mononuclear cells invade cartilaginous structures of sacroiliac joints and intervertebral discs leading to destruction and ankylosis.[41] T-cell responses to aggrecan have been seen not only in spondyloarthritides but also in other arthritides.[42] Both CD4+[43] and CD8+ T-cell responses[44] to aggrecan and collagen-derived peptides have been reported in peripheral blood and synovial fluid specimens of patients with ankylosing spondylitis.[45] Immunohistological studies on sacroiliac joint biopsies have shown cellular infiltrates, including T cells and macrophages (figure 1).[36,46] Immunohistological examination of femoral heads of patients with this disease

undergoing total hip replacement[47] showed infiltrates of CD4+ and CD8+ T cells at the cartilage-bone interface, which are possibly dependent on the presence of cartilage. Immunohistological examination of zygapophysal joints from patients with this disease undergoing spinal surgery because of severe kyphosis[48] showed persistence of inflammation even in longstanding disease (figure 1).

Both innate and adaptive immune responses could have a role in spondyloarthritides. The finding that tumour necrosis factor (TNF)-α is overexpressed in sacroiliac joints (figure 1)[46] provided a strong rationale for the use of TNF-inhibitors, which are very effective in spondyloarthritides.

The remodelling of bone that explains squaring of vertebral bodies in ankylosing spondylitis is histologically based on acute and chronic spondylitis with destruction and simultaneous rebuilding of the cortex and spongiosa of the vertebral bodies. The development of square vertebral bodies is based on a combination of a destructive osteitis and repair.[49] The process of joint ankylosis partly recapitulates embryonic endochondral bone formation in a spontaneous model of arthritis in DBA-1 mice. Bone growth factors such as bone morphogenetic protein signalling are key molecular pathways associated with pathological changes.[50] Systemic gene transfer of noggin, an antagonist of bone morphogenetic protein, is effective both as a preventive and therapeutic strategy in this mouse model, since noggin interferes with enthesial progenitor cell proliferation. Immunohistochemical staining for phosphorylated smad1/5 in entheseal biopsies of patients with spondyloarthritides shows active bone morphogenetic protein signalling in similar target cells,[51] which suggests a role for these proteins in the pathogenesis of ankylosing spondylitis. In psoriatic arthritis[52] and ankylosing spondylitis,[47] an increased osteoclast activity has been reported. Osteoclasts are key in inflammation-associated bone loss in rheumatic diseases.[53]

Patients with ankylosing spondylitis are frequently given non-steroidal anti-inflammatory drugs (NSAIDs), including cyclo-oxygenase (COX)-2-selective inhibitors. COX-2 is an inducible enzyme that converts arachidonic acid to prostaglandin E2, a modulator of bone metabolism.[54] The inhibition of radiographic progression by continuous intake of NSAIDs[55] could be explained by the inhibition of prostaglandins by these drugs. However, this finding needs to be confirmed. Several in-vitro studies and work in animals showed impaired bone healing in the presence of NSAIDs.[56] The steps associated with bone healing include an inflammatory response, bone resorption, and new bone formation. Prostaglandins have been shown to elicit and participate in inflammatory responses, increase osteoclast activity and subsequent bone resorption, and raise osteoblast activity and new bone formation. Through inhibition of COX and subsequently prostaglandins, NSAIDs could inhibit new bone formation. This inhibition is clinically used to prevent ossification after surgery, and there may be differences related to the degree of COX-1 and COX-2 inhibition.[57]

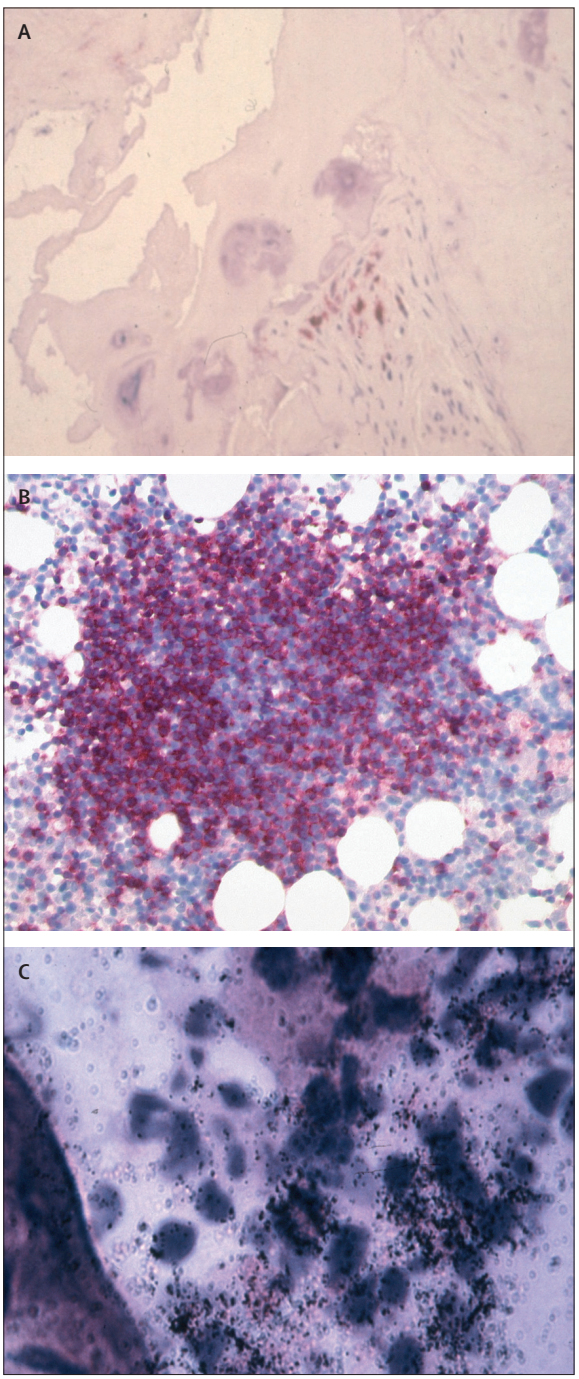

Figure 1: **Immunohistology in ankylosing spondylitis**
(A) T-cell infiltrate in a biopsy specimen obtained from the sacroiliac joint of a patient with ankylosing spondylitis. Reproduced from Bollow et al[36] with permission from BMJ Publishing Group. (B) Immunohistology of bone marrow close to a zygapophyseal joint of a patient with ankylosing spondylitis who underwent spinal surgery for correction of rigid hyperkyphosis. The presence of CD3+ T cell aggregates indicates ongoing inflammation in longstanding disease. Reproduced from Appel et al[48] with permission from Wiley-Liss, a subsidiary of John Wiley & Sons. (C) TNFa mRNA (in-situ hybridisation) in a biopsy specimen obtained from the sacroiliac joint of a patient with ankylosing spondylitis. Reproduced from Braun et al[37] with permission from Wiley-Liss, a subsidiary of John Wiley & Sons.

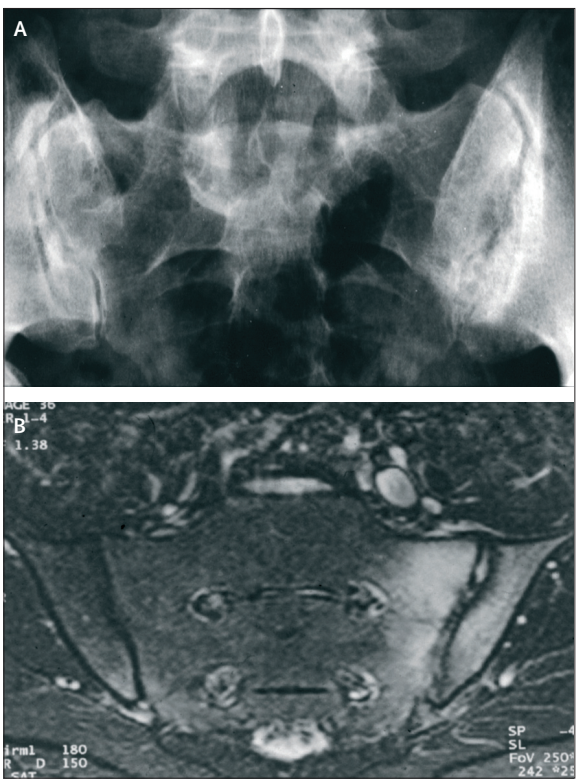

Figure 2: **Pelvic radiograph and MRI of the sacroiliac joint in two different patients with spondyloarthritis**
Radiograph showing chronic changes in the sacroiliac joints in a patient with ankylosing spondylitis (A) and MRI (STIR technique) showing active changes (sacroiliitis) in a patient with undifferentiated spondyloarthritis (B).

Possible combination of clinical, laboratory, or imaging SpA features	Post-test probability
IBP plus family history	51%
IBP plus heel pain	35%
IBP plus uveitis	54%
IBP plus synovitis	39%
IBP plus dactylitis	42%
IBP plus family history plus heel pain	78%
IBP plus uveitis plus NSAID*	85%
IBP plus heel pain plus synovitis plus alternating buttock pain	89%
IBP plus family history plus heel pain plus NSAID*	95%
IBP plus heel pain plus HLA-B27	83%
IBP plus NSAIDs* plus HLA-B27	88%
IBP plus heel pain without HLA-B27	6%
IBP plus NSAIDs* without HLA-B27	8%
IBP plus dactylitis plus ESR/CRP	62%
IBP plus HLA-B27 plus ESR/CRP	78%
IBP plus HLA-B27 without ESR/CRP	47%
IBP plus HLA-B27 plus MRI	93%
IBP plus HLA-B27 without MRI	14%
IBP plus heel pain plus HLA-B27 without MRI	35%

The pretest probability of low back pain is assumed to be 5%. IBP=inflammatory back pain. SpA=axial spondylarthritis. CRP=C-reactive protein. *A good response to NSAIDs is needed. Adapted from Radwaleit et al[16] with permission of BMJ Publishing Group.

Table: **Probability of axial spondylitis with or without various combinaions of features in patients with low back pain**

Genetics

Although HLA B27 itself is the most important gene predisposing to ankylosing spondylitis, there is clear evidence of association of other genes with susceptibility to this disease. Studies (in twins)[25] suggest a contribution of HLA B27 of only about 20–30% of the total genetic risk in this disease, whereas the whole MHC contributes about 40–50%. The concordance rate is 63% for B27-positive monozygotic twin pairs, and 23% for dizygotic twin pairs. Furthermore, HLA B27-positive individuals with a first-degree relative having ankylosing spondylitis have a six to 16 times greater risk of developing the disease themselves than do B27-positive individuals with no family history.[25,58] All these data suggest that non-B27 familial factors have a strong effect on the risk of developing this disease.

Besides HLA B27, other MHC genes such as HLA B60 and HLA DR1 seem to be associated with ankylosing spondylitis but they are of minor importance. The TNFα gene is another candidate gene located within the MHC, but a major role of TNF polymorphisms in patients with this disease is unlikely.[59] Genome-wide linkage screens have suggested several additional genetic markers distributed on different chromosomes,[60,61] none of which is conclusive. There is some evidence for the presence of a non-MHC susceptibility locus for spondyloarthritides mapping to 9q31-34.[62] No linkage of the X chromosome (suspected to be a candidate gene because of the sex bias of ankylosing spondylitis), has been reported.[63] Suggestive gene markers include genes associated with diseases that predispose to spondyloarthritides such as psoriasis and inflammatory bowel disease, or markers that could encompass genes relevant for immune responses, such as antigen processing and presentation or cytokine responses. For example, occurrence of acute anterior uveitis might be associated with a gene region located on chromosome 9.[64] The interleukin-1 gene cluster located on chromosome 2 is involved in ankylosing spondylitis,[65] but which exact genes are causatively involved is as yet unclear. NOD 2 (nucleotide-binding oligomerisation domain protein 2, CARD15) genotypes located on chromosome 16 are associated with Crohn's disease but not with primary ankylosing spondylitis.[66] Other candidate gene analyses in this disease, such as on TGFβ (transforming growth factor β) and interleukin-6 polymorphisms, were negative. Thus, there is a definite contribution of genes other than HLA B27. Most genetic studies are on susceptibility but there are also some on severity that also suggest a strong genetic rather than an environmental effect.[67]

Diagnosis and classification

Radiography

Sacroiliitis is a hallmark of ankylosing spondylitis, especially in earlier disease stages. It has become a major means for the development of classification criteria because of its very high prevalence in patients with ankylosing spondylitis. The first criteria set for classification, developed in 1961 in

Rome, Italy,[68] did not need radiographs of the sacroiliac joints to make a diagnosis, but in the 1966 New York (USA) criteria radiographic evidence of sacroiliac joint changes were included.[69] The proposed grading system scored a healthy radiograph of the sacroiliac joints as 0, suspicious changes as 1, minor changes as 2, moderate changes as 3 (figure 2), and ankylosis as 4. The last modification of the New York criteria[70] introduced the clinical parameter of inflammatory back pain, and changed the criterion restriction of chest expansion by age and sex adjustment of the normal values (panel 1). These 1984 criteria are used not only for classification, but also for diagnosis of patients with ankylosing spondylitis.

Since radiographs of the sacroiliac joints could appear normal in the early phase of disease, structural changes might become apparent only after some years, which is relevant for a rather large proportion of patients with this disease.[71,72] With the introduction of MRI the fact that radiography of the sacroiliac joints detects the structural results of inflammation (cartilage and bone damage) rather than inflammation itself has become obvious. Accordingly, the MRI technique allows for the detection of inflammation in the sacroiliac joints in patients early in the course of their disease when no chronic changes are detectable.[37] This latency in the radiographic detection of chronic changes in the sacroiliac joints contributes to the diagnostic delay in ankylosing spondylitis.[1,73]

Clinical criteria

To allow for an earlier diagnosis of spondyloarthritides for patients with predominant axial or peripheral manifestations of disease, two sets of criteria were developed about 15 years ago which are more clinically based—the European Spondyloarthropathy Study Group[18] and the Amor criteria.[74] Radiographic evidence of sacroiliitis was included in both criteria sets as an optional item but not as a prerequsite for diagnosis. Both sets work well as classification criteria—validation studies in various populations showed a sensitivity and specificity of about 85%.[75] However, even though these criteria sets have also been used to make a diagnosis in clinical practice because of few alternatives, all sets for ankylosing spondylitis and spondyloarthritis were developed for classification but not for diagnostic purposes. The process of classification implies a diagnostic selection beforehand, and, by contrast with diagnostic criteria, knowledge of the pretest probability of having the disease is not necessary.[72] The use of classification criteria for diagnosis could result in an overestimation or underestimation of the frequency of the disease.

A systematic approach to diagnose patients presenting with early predominantly axial spondyloarthritis has been developed.[72,76] The first step is an estimation of the pretest probability of the disease.[77] In a cohort of patients with chronic low back pain in a primary care physician setting, spondyloarthritis was diagnosed in 5% of cases, which is the assumed pretest probability of this disease.[78] The likelihood of a diagnosis of spondyloarthritis is best if at least three clinical, laboratory, or imaging indices are positive (table).[72,76] The pretest probability could be different in other settings.

***Panel 2:* New criteria for inflammatory back pain in young to middle-aged adults (<50 years) with chronic back pain.**

- Morning stiffness >30 minutes
- Improvement in back pain with exercise but not with rest
- Awakening because of back pain during the second half of the night only
- Alternating buttock pain

The criteria are fulfilled if at least two of four of the parameters are present (sensitivity 70·3%, specificity 81·2%). Adapted from Rudwaleit et al[80] with permission from Wiley-Liss, a subsidiary of John Wiley & Sons.

The clinical symptom of inflammatory back pain is important for the diagnosis of spondyloarthritis and ankylosing spondylitis,[79] including early and late stages, and also classification.[18,70,74] However, because of restricted sensitivity and specificity of inflammatory back pain, a combination with other indices suggestive of spondyloarthritis is needed. A novel set of classification criteria for inflammatory back pain has been developed on the basis of a controlled study showing a specificity of 81% and a sensitivity of 70% if two of four indices are positive.[80] However, the diagnostic yield is better than this result when three of four indices are fulfilled (panel 2).

The development of criteria allowing for an early diagnosis of ankylosing spondylitis is important to alert primary care physicians to consider spondyloarthritis in patients with chronic back pain. To establish when to refer patients to a rheumatologist for diagnosis is of similar relevance. Screening indices for early referral of patients with ankylosing spondylitis by primary care physicians have been proposed.[81] A diagnosis of spondyloarthritis was predicted in every third to fifth patient with chronic (>3 months) low back pain that started at an age younger than 45 years who either has the clinical symptom of inflammatory back pain, carries HLA B27, or has sacroiliitis shown by imaging. How such criteria perform in daily clinical practice remains to be seen.

Laboratory tests

There are two main laboratory indices that are potentially relevant for a diagnosis of spondyloarthritis—HLA B27 and C-reactive protein.[76] However, the role of the erythrocyte sedimentation rate is less clear. HLA B27 is an important factor for diagnosis of early spondyloarthritis. The performance of the HLA-B27 test depends on the population prevalence of HLA B27, which varies for different races. There is no need to measure HLA-B27 subtypes in white patients, but subtyping might be needed for Chinese patients, in whom some subtypes (eg, HLA-B*2706) are not associated with ankylosing spondylitis. The correlation of disease activity with laboratory indices of inflammation is restricted. Only half of patients with this disease have raised C-reactive protein concentrations.[82]

Imaging

Imaging is crucial for the diagnosis and classification of spondyloarthritides, especially ankylosing spondylitis, because conventional radiography is sufficiently sensitive in established disease since more than 95% of patients have structural changes in the sacroiliac joints (figure 2).[83] Furthermore, the detection of typical syndesmophytes (figure 3) could be useful for diagnosis in individual patients. These possible osteoproliferative changes, however, do not tend to take place early in the course of the disease. Therefore, MRI, with its capacity to visualise active inflammation, has been of much additional diagnostic benefit in early disease when a field strength of T2 for fat saturated and short T1 inversion recovery (STIR) or a field strength of T1 after application of contrast agents such as gadolinium-diethylenetriamine penta-acetic acid are used. For screening purposes, contrast agents are not necessary since the STIR technique is sufficient.[84]

MRI has proved especially useful for identification of early sacroiliitis (figure 2)[37] and spondylitis (figure 3),[85] including patients with undifferentiated spondyloarthritis.[86] MRI of the sacroiliac joints can predict the development of structural radiographic changes in these joints with a positive predictive value of 60% 3 years before they occur.[87] MRI measurements of the spine (figure 3)[88] as assessed by a new scoring system are sensitive to change in patients with ankylosing spondylitis and inflammatory back pain on antiTNF therapy.[89,90] The assessment of chronic changes by MRI[91] is still under investigation, but conventional radiography is more sensitive to detect structural changes than is MRI.[92] Therefore, a radiograph of the sacroiliac joints is always needed, especially at early disease stages because 20–30% of patients within the first 2 years of inflammatory back pain will already have developed structural changes. MRI is not only useful for detection of enthesitis and synovitis in the axial skeleton but also in peripheral joints and entheses,[93] which are also well assessed by ultrasonography.[94]

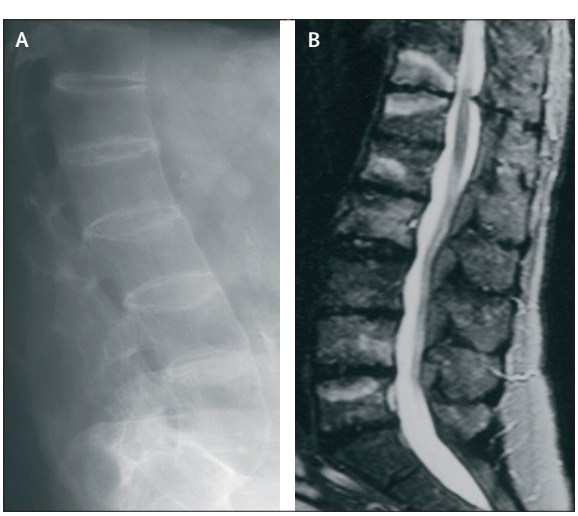

Figure 3: **Chronic and active changes in the lumbar spine of a patient with ankylosing spondylitis**
Syndesmophytes shown on radiograph (A) and spondylitis and spondylodiscitis shown by T2 weighted MRI (B).

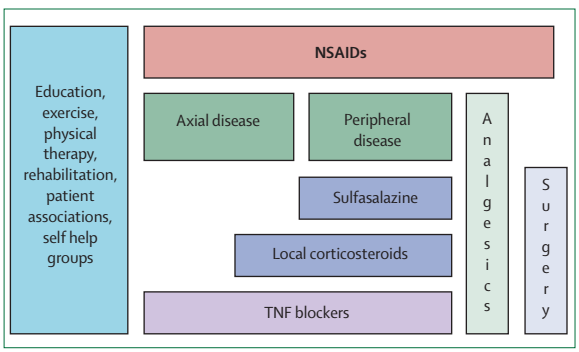

Figure 4: **Flow chart of the ASsessment of Ankylosing Spondylitis (ASAS) and European League Against Rheumatism (EULAR) recommendations for the management of ankylosing spondylitis.**
Adpated from Zochling et al[98] with permission from BMJ Publishing Group. NSAIDs=non-steroidal anti-inflammatory drugs.

The cost-effectiveness of these imaging techniques in early disease has not yet been assessed. Nevertheless, from a clinical point of view there seems little doubt that MRI should be included in future classification and diagnostic criteria for early spondyloarthritides. In the assessment of patients with possible spondyloarthritides and low back pain, differentiation between the search for active and acute changes from chronic changes is important. For active and acute changes, MRI with appropriate sequences such as STIR are useful, and in centres of excellence scintigraphy is also of use, especially when the indication includes screening for other affected sites. For the detection of chronic changes in the sacroiliac joints CT is most useful;[95] however, the technique should not be used routinely because of a high exposure to radiation. Conventional radiography is still the gold standard for the detection of chronic structural changes in the sacroiliac joints and spine. The modified Stoke ankylosing spondylitis spinal score is the most useful scoring method for assessment of spinal damage in clinical studies.[96] In this system, syndesmophytes are most important. Radiographic damage at baseline is the strongest predictor of future structural changes.[97]

Management

Ten main recommendations for the management of ankylosing spondylitis have been proposed by a combined ASsessment in Ankylosing Spondylitis working group (ASAS) and European League Against Rheumatism (EULAR) task force (figure 4).[98] Briefly, the treatment of ankylosing spondylitis should be tailored according to the manifestations of the disease at presentation, severity of symptoms, and several other features that include the wishes and expectations of the patient. The disease monitoring of patients should include history, clinical features, laboratory tests, and imaging. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity, and drugs. The best treatment needs a combination of non-pharmacological

and pharmacological treatment methods, including education and physical therapy. AntiTNF therapy should be given according to ASAS recommendations.[99] Joint replacement has to be considered in patients with radiographic evidence of advanced hip involvement who have refractory pain and disability. Spinal surgery is useful in selected patients with symptoms and disability because of disabilitating posture or instable spine.

Basic principles of treatment

The standard treatment of spinal symptoms for patients with ankylosing spondylitis has consisted of NSAIDs[100]and structured exercise programmes[101] for decades. Whether and to what extent physical therapy and exercise are beneficial in every stage of the disease (eg, in very active disease) is unknown. Disease activity, especially the degree of spinal inflammation, function, and damage, probably affects the outcome of physical therapy and regular exercise. Non-pharmacological therapy consists of spa treatment,[102] education, and self-help groups, as well as physical therapy. A Cochrane review[103] showed that there is little evidence for effectiveness of non-pharmacological intervention, but there is strongly positive expert opinion. Although the general effect size is believed to be rather small, it is clear from clinical experience that individual patients with ankylosing spondylitis may have definite benefit from intensive physiotherapy. Intensive spa therapy has proved more effective than standard prescriptions of exercises in an outpatient setting, especially after several months.[102]

NSAIDs

In general, NSAIDs work rather well in patients with ankylosing spondylitis. A good response to NSAIDs has even been identified as a diagnostic sign for spondyloarthritides,[74] although a state of non-responsiveness to these drugs might identify those with a poor prognosis.[19] Clinical experience suggests that patients with active disease should be continuously given NSAIDs in a dose sufficient to control pain and stiffness. Some researchers[55] have even suggested that continuous dosing with NSAIDs rather than the usual on-demand prescription decelerates radiographic progression over 2 years. However, NSAIDs, including COX-2 inhibitors, are known to have gastrointestinal and possible cardiovascular toxic effects,[104] which could restrict their use. Furthermore, about half of patients with this disease report insufficient control of their symptoms by NSAIDs alone.[98]

Disease-modifying antirheumatic drugs

The use of disease-modifying antirheumatic drugs for the treatment of axial disease in spondyloarthritides has been rather disappointing. Treatments that are effective in suppression of disease activity and slowing of progression in rheumatoid arthritis have notably failed to affect patients with spondyloarthritides, especially those with spinal disease.[90,98] Sulfasalazine improves peripheral arthritis associated with spondyloarthritis, but not spinal pain.[105,106] However, there are differences between the trials related to disease duration and the proportion of patients with peripheral arthritis. Thus, the effectiveness of sulfasalazine in earlier disease stages might differ from that at later stages. Indeed, in a controlled trial[107] of sulfasalazine in undifferentiated spondyloarthritis and early ankylosing spondylitis, some improvement of spinal pain was noted since patients with inflammatory back pain but no peripheral arthritis had substantially more improvement in disease activity than did the placebo group despite use of fewer NSAIDs.[107] However, all patients improved, and definite conclusions are difficult to draw.

Methotrexate is generally used in patients with rheumatoid arthritis to improve symptoms and slow progression of erosive disease. However, such improvement is not seen in ankylosing spondylitis, suggesting

***Panel 3:* Updated assessment in ankylosing spondylitis (ASAS) criteria for antiTNF therapy in ankylosing spondylitis**

Diagnosis

Patients who usually fulfil modified New York criteria (panel 1) for definitive AS

Active disease

Active disease for at least 4 weeks

BASDAI ≥4 (range 0–10) and an expert opinion*

Treatment failure

All patients should have had adequate therapeutic trials of at least two NSAIDs. An adequate therapeutic trial is defined as:

- Treatment for at least 3 months at maximum recommended or tolerated anti-inflammatory dose unless contraindicated
- Treatment for <3 months where treatment was withdrawn because of intolerance, toxicity, or contraindications

Patients with pure axial features do not have to take DMARDs before antiTNF therapy can be started

Patients with symptomatic peripheral arthritis should have undergone at least one local corticosteroid injection if appropriate and should have responded insufficiently

Patients with persistent peripheral arthritis must have had a therapeutic trial of sulfasalazine†

Patients with symptomatic enthesitis must have failed appropriate local treatment

All three of the above points have to be fulfilled before treatment with TNF blockers is started.

Contraindication

Women who are pregnant or breastfeeding; effective contraception must be practised

Active infection

Patients at high risk of infection including:

- Chronic leg ulcer
- Previous tuberculosis
- Septic arthritis of a native joint within the past 12 months
- Sepsis of a prosthetic joint within the past 12 months, or indefinitely if the joint remains in situ
- Persistent or recurrent chest infections
- Indwelling urinary catheter

History of lupus or multiple sclerosis

Malignant disease or premalignant states excluding:

- Basal cell carcinoma
- Malignant diseases diagnosed and treated more than 10 years previously (where the probability of total cure is very high)

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Assessment of disease

ASsessment of Ankylosing Spondylitis (ASAS) core set for daily practice

- Physical function (BASFI or Dougados functional index)
- Pain (VAS, last week, pain at night and spine pain in general)
- Spinal mobility (chest expansion and modified Schober and occiput to wall distance and lateral lumbar flexion)
- Patient's general assessment (VAS, last week)
- Stiffness (duration of morning stiffness, spine, last week)
- Peripheral joints and entheses (number of swollen joints [44 joints count], enthesitis score such as developed in Maastricht, Berlin, or San Francisco)
- Acute phase reactants (ESR or CRP)
- Fatigue (VAS)

BASDAI

- VAS overall level of fatigue/tiredness past week
- VAS overall level of AS neck, back, or hip pain past week
- VAS overall level of pain/swelling in joints other than neck, back, or hips past week
- VAS overall discomfort from any areas tender to touch or pressure past week
- VAS overall level of morning stiffness from time of awakening past week
- Duration and intensity (VAS) of morning stiffness from time of awakening (up to 120 mins)

Assessment of response

Responder criteria

- BASDAI: 50% relative change or absolute improvement of 20 mm (0–100) and expert opinion: continuation yes/no

Time of assessment

- Between 6 and 12 weeks

VAS=visual analogue scale; all VAS can be replaced by a numerical rating scale (NRS). BASDAI=Bath ankylosing spondylitis disease activity index. BASFI=Bath ankylosing spondylitis functional index. AS=ankylosing spondylitis. *A physician, usually a rheumatologist, with expertise in inflammatory back pain and the use of biological substances. Expert should be locally defined. An expert opinion consists of both clinical features (history and examination) and either serum acute-phase reactant concentrations or imaging results, such as radiographs showing rapid progression or MRI scans indicating continuing inflammation. †Treatment for at least 4 months at standard target dose or maximum tolerated dose unless contraindicated or not tolerated. Treatment for less than 4 months, in which treatment was withdrawn because of intolerance or toxicity or contraindicated. Adapted from Braun et al[99] with permission from BMJ Publishing Group.

another pathomechanism. A systematic review[108] of the use of methotrexate in ankylosing spondylitis showed that there was no evidence for an effect on inflammatory back pain and inconclusive evidence of effectiveness for peripheral joint disease. The only randomised controlled trial[109] of this drug in patients with ankylosing spondylitis failed to show a significant effect of oral methotrexate (7·5 mg per week) on spondylitis, but there was some improvement of peripheral arthritis. A 16-week open label trial[110] of methotrexate, 20 mg subcutaneously, in 20 patients with ankylosing spondylitis did not show any effect on axial symptoms and only some improvement in peripheral symptoms. In contrast to these findings, many rheumatologists are still using methotrexate for ankylosing spondylitis because there used to be no other options. The differences in response between peripheral and axial symptoms might be explained by predominant synovitis for peripheral manifestations and predominant enthesitis for axial manifestations.

Similarly, leflunomide is effective in treatment of symptoms and slowing radiographic change in rheumatoid arthritis. In ankylosing spondylitis, leflunomide was not effective for axial manifestations,[111,112] but patients with peripheral arthritis had some benefit.[111] However, this drug is effective in patients with psoriatic arthritis.[113] Maksymowych and co-workers[114] suggested that bisphosphonates could be useful for spinal symptoms for patients with ankylosing spondylitis. However, other studies with pamidronate failed to show a similar effect.[115] Thalidomide was also used with some success[116] but is regarded as too toxic for widespread use.

TNF blockers

The introduction of TNF blockers has been the most substantial development in the treatment of ankylosing spondylitis and other spondyloarthritides in the past few years.[98] Three such agents are now approved for ankylosing spondylitis: the monoclonal chimeric antibody infliximab, which is given intravenously in a dose of 3–5 mg per kg every 6–8 weeks (approved regimen is 5 mg/kg every 6–8 weeks), the fully humanised monoclonal adalimumab which is given subcutaneously in a dose of 40 mg every other week, and the 75 kD TNF receptor fusion protein etanercept given subcutaneously in a dose of 50 mg once per week or 25 mg twice per week. The success of antiTNF treatment in spondyloarthritis is probably a class effect. There is some evidence that this treatment works even better in spondyloarthritis than in rheumatoid arthritis.[117]

Large randomised, placebo-controlled trials[118,119] of infliximab, etanercept,[120,121] and adalimumab[122,123] in patients with ankylosing spondylitis have shown impressive short-term improvements in spinal pain, function, and inflammatory markers. As experience with these therapies increases to 2–5-year trials,[124,125] effectiveness could persist with continuing treatment, and more than a third of patients are in remission. These trials show substantial improvement of pain, function, and disease activity in patients with active disease compared with placebo. Indeed, all outcome measures including Bath ankylosing spondylitis disease activity index (BASDAI), functional index (BASFI), and metrology index (BASMI), and the physical component of the SF-36 health survey improved greatly after 24 and 102 weeks. The improvement usually starts within 2 weeks of therapy and C-reactive protein concentrations also tend to decrease rapidly.

Alongside the reported long-term effectiveness and safety of TNF blockers in ankylosing spondylitis, the loss of response after cessation of continuous therapy with infliximab for 3 years is important,[126] but readministration has been successful and has not caused problems. Treatment with infliximab decreases active spinal inflammation as detected by MRI.[89,90] No substantial radiological progression of disease as assessed by the modified Stoke ankylosing spondylitis spine score (SASSS), which scores radiographs in ankylosing spondylitis,[127] was seen in a few patients with this disease who were given infliximab for 2 years.[128]

The effectiveness of etanercept in this disease was also seen,[129] and the higher percentage of assessment of

ankylosing spondylitis responders in the active therapy group was confirmed in randomised controlled trials,[120,121] in which 20–30% of patients continued treatment with disease-modifying antirheumatic drugs and corticosteroids. After several months without etanercept therapy[129,130] all patients had had a relapse of disease activity, but reintroduction of the treatment was effective and safe. The clinical effectiveness of etanercept was also confirmed by MRI.[131] Adalimumab was also proved effective in patients with ankylosing spondylitis in a pilot study,[122] and this result was confirmed in a randomised controlled trial[123] in which the pain of some patients with even advanced spinal ankylosis also improved.

The first pilot studies[129,132] of infliximab and etanercept in undifferentiated spondyloarthritis have also been successful. Similarly to infliximab, etanercept and adalimumab are effective for peripheral joint and skin symptoms in patients with psoriatic arthritis.[133] Etanercept is effective for rheumatic manifestations in inflammatory bowel disease for joint and spine but not gut symptoms.[134] Furthermore, etanercept has no effect on inflammatory bowel disease,[135] unlike infliximab, which is approved for Crohn's disease[136] and ulcerative colitis.[137] Thus, etanercept is not recommended for the small spondyloarthritis subgroup with concomitant inflammatory bowel disease. There could also be a difference in the prevention and treatment of anterior uveitis.[138]

Clinical disease activity and spinal inflammation as detected by MRI are substantially reduced by TNF blockers, as shown after short-term and long-term antiTNF therapy.[122,131,139] Whether antiTNF treatment is able to stop radiographic progression has not yet been proven. In a disease with pronounced long-term functional disability due to the development of syndesmophytes and spinal ankylosis,[14] any treatment that does not only suppress disease activity but also prevents or decelerates structural damage and decline of function will be of great importance for patient care. Recommendations on which patients with ankylosing spondylitis should be given TNF-blockers are especially needed because of possible side-effects and the high costs of these drugs. Thus, patients with the best risk to benefit ratio should be treated preferentially. An international assessment of ankylosing spondylitis consensus statement for the use of antiTNF agents in patients with this disease was reported in 2003[140] and updated in 2006.[99] Panel 3 shows a summary of these recommendations for the initiation of antiTNF α therapy. Prediction of response is difficult. However, it seems clear that patients early in the course of their disease, with raised C-reactive protein concentrations,[141] positive MRI findings, or less structural damage are more likely to respond than are patients with advanced disease, but overall all patient subgroups could benefit from this treatment.

Anakinra is a recombinant human interleukin-1 receptor antagonist, which is directed at a different cytokine in the inflammatory response than TNF blockers. By contrast with TNF, whether interleukin-1 is present in sacroiliac joints is unclear. Two open studies[142,143] of anakinra in ankylosing spondylitis showed partly conflicting results. Other biological compounds have not been tested so far.

Socioeconomics

Cost-effectiveness is an issue when expensive treatments are discussed. Despite the high costs, the clinical benefits[118] and improvements in quality of life in patients with ankylosing spondylitis given infliximab result in lower disease-associated costs than does standard care, which translates to a short-term cost of about US$70 000 (GB£35 000) per quality-adjusted life year (QALY) gained[144]—an amount societies might be willing to pay. However, the calculated costs were higher than this figure in other analyses.[145] When modelling for long-term therapy, with yearly disease progression of 0·07 of the BASFI in the sensitivity analysis, the cost per QALY gained is reduced to less than $20 000 (£10 000).[144] Until long-term data on disease progression with antiTNF therapy in patients with ankylosing spondylitis are available, these conclusions remain hypothetical, but the costs for antiTNF therapy seem to fall well inside what is thought of as cost effective. Furthermore, the daily productivity of patients with active disease, which was substantially associated with functional impairment and disease activity, greatly improved with infliximab, and this was associated with reduced workday loss in employed patients.[146]

Conflict of interest statement

J Braun and J Sieper have received consultancy and speaker's fees, honoraria, and research funding from several companies including Abbott, Amgen, Centocor, MSD, Novartis, Pfizer, Roche, Schering-Plough, and Wyeth but they had no conflict when writing this paper.

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Adolescent Health 4

Interventions to reduce harm associated with adolescent substance use

J W Toumbourou, T Stockwell, C Neighbors, G A Marlatt, J Sturge, J Rehm

Summary

A major proportion of the disease burden and deaths for young people in developed nations is attributable to misuse of alcohol and illicit drugs. Patterns of substance use established in adolescence are quite stable and predict chronic patterns of use, mortality, and morbidity later in life. We integrated findings of systematic reviews to summarise evidence for interventions aimed at prevention and reduction of harms related to adolescent substance use. Evidence of efficacy was available for developmental prevention interventions that aim to prevent onset of harmful patterns in settings such as vulnerable families, schools, and communities, and universal strategies to reduce attractiveness of substance use. Regulatory interventions aim to increase perceived costs and reduce availability and accessibility of substances. Increasing price, restricting settings of use, and raising legal purchase age are effective in reducing use of alcohol and tobacco and related harms. Screening and brief intervention are efficacious, but efficacy of a range of treatment approaches has not been reliably established. Harm-reduction interventions are effective in young people involved in risky and injecting substance use.

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In many countries, overdoses of alcohol and other drugs compete with road crashes as leading causes of death in young people.[1] The substantial contribution of alcohol and other drugs to suicide, homicide, a range of injuries, poisoning, and the spread of infectious disease is also now well established.[2,3] Hazardous alcohol use alone has been estimated to cause 31·5% of all deaths in 15–29-year-old men in the developed world and 86% of the 3·6 million substance-related deaths of 15–29-year-old men and women worldwide (table 1). Psychoactive substance use occurs in all known societies, with heavy episodic or binge use being especially common among young people,[5–8] so that the risk of these adverse acute consequences can be seen as a function of societal context as well as individual susceptibility. In 2000, the use of alcohol and illicit drugs was estimated to contribute 9·8% of the total global burden of disease for people aged 15–29 years (table 2). This burden fell disproportionately on male individuals and people living in developed countries. In economically developed countries, 23·3% of the global burden of disease is contributed to by alcohol (18·5%) and illicit drugs (4·9%). No evidence exists of significant health benefits from moderate alcohol consumption for young adults to offset these adverse effects.[2,9] There are several social and legal consequences of substance use for young people, including work and travel restrictions as a consequence of a

Search strategy

We aimed to complete an integrative summary of current knowledge of the effectiveness of interventions designed to prevent and reduce the major harms associated with adolescent substance use. The co-authors, selected because of their expertise in specific areas of work in this area, supplemented recently completed comprehensive systematic reviews[53,57] using the PubMed, Psychlit, and Google scholar electronic databases, and keyword and text searches relevant to (adolescen*) and (alcohol or drug or substance and use or abuse) and (review) to locate additional systematic review papers published in the past 2 years. The conclusions of review papers were included where they met quality standards for systematic selection and methodological evaluation.[27,28] Authors were asked to integrate review findings citing key evidence from well-done and influential empirical studies and noting implications for research and practice. A judgment of intervention efficacy required overall positive evidence from well-controlled outcome evaluations. Interventions were judged as effective where outcomes were maintained outside controlled research contexts in real-world service delivery conditions.[29]

We used a broad definition of substance use, which included adolescent use of alcohol (ethanol) and tobacco, and non-medical use of prescription medications (including analgesics and sedatives) and illicit drugs including cannabis, heroin, cocaine, amphetamine-type substances, and hallucinogens. As relevant to substance use, adolescence was defined broadly to refer to the period before puberty (around age 10 years) through to the achievement of financial independence in emerging adulthood (around late 20s).[30] Literature relevant to harms, current substance use trends, and influences was overviewed to provide a context for intervention.

We summarise current understanding of intervention opportunities and the conclusions of evaluation studies that have examined effects in modification of behaviour, reduction of harm, and savings in costs.

	Alcohol			Illegal drugs			Alcohol and illegal drugs		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Developed countries*	72 (31·5%)	10 (12·5%)	82 (26·7%)	9 (3·9%)	3 (4·1%)	12 (3·9%)	81 (35·3%)	13 (16·6%)	94 (30·6%)
Emerging economies*	107 (18·3%)	12 (4·5%)	119 (13·9%)	13 (2·3%)	4 (1·6%)	18 (2·1%)	120 (20·6%)	17 (6·1%)	137 (16·0%)
Developing countries*	70 (6·3%)	14 (1·1%)	84 (3·5%)	12 (1·1%)	3 (0·2%)	15 (0·6%)	82 (7·4%)	17 (1·3%)	99 (4·1%)
Worldwide†	249/1922 (13·0%)	36/1672 (2·2%)	286/3594 (7·9%)	34/1922 (1·8%)	11/1672 (0·6%)	45/3594 (1·3%)	284/1922 (14·8%)	47/1672 (2·8%)	331/3594 (9·2%)

Authors' estimates derived from Ezzati and colleagues[3] using their definitions of global regions. Overlap between harm caused by alcohol and by illegal drugs can result in small overestimation (<3%).[4] Numbers may not add up due to rounding. *Percentage of total deaths in people aged 15–29 years for the relevant region in parentheses. †Substance-attributable deaths worldwide/total deaths worldwide for all conditions (% of total due to alcohol and other drugs).

Table 1: **Substance-attributable deaths in developed countries, countries with emerging economies, and developing countries for people aged 15–29 years in 2000 (thousands)**

	Alcohol			Illegal drugs			Alcohol and illegal drugs		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Developed countries	5655 (26·6%)	1244 (7·7%)	6898 (18·5%)	1326 (6·2%)	487 (3·0%)	1814 (4·9%)	6981 (32·9%)	1731 (10·7%)	8712 (23·3%)
Emerging economies	8569 (17·7%)	1393 (3·8%)	9961 (11·7%)	1459 (3·0%)	437 (1·2%)	1896 (2·2%)	10 028 (20·8%)	1830 (4·9%)	11 858 (13·9%)
Developing countries	4221 (5·9%)	798 (0·9%)	5019 (3·2%)	1571 (2·2%)	410 (0·5%)	1981 (1·3%)	5792 (8·2%)	1208 (1·4%)	7000 (4·4%)
Worldwide†	18 444/140 519 (13·1%)	3434/139 867 (2·5%)	21 879/280 386 (7·8%)	4356/140 519 (3·1%)	1335/139 867 (1·0%)	5691/280 386 (2·0%)	22 800/140 519 (16·2%)	4769/139 867 (3·4%)	27 570/280 386 (9·8%)

Authors' estimates derived from Ezzati and colleagues[3] using their definitions of global regions. Overlap between harm caused by alcohol and by illegal drugs can result in small overestimation (<3%).[4] Numbers may not add up due to rounding. *Percentage of total DALYs lost in people aged 15–29 years for the relevant global region in parentheses. †Substance-attributable DALYs lost/total DALYS lost worldwide for all conditions (% of total caused by alcohol and other drugs).

Table 2: **Substance-attributable disability-adjusted life years (DALYs) in developed countries, countries with emerging economies, and developing countries for people aged 15–29 years in 2000 (thousands)**

conviction for possession of cannabis in some jurisdictions. For example, a cannabis conviction can result in exclusion from work with children in some Australian health jurisdictions and disqualification from legal entry into the USA.[10]

Substance use disorders in adolescence mostly include harmful use (ICD-10 F10–F19),[11] and abuse (DSM-IV 291.9, 292.89, 292.9),[12] whereas dependence[12] remains rare until late adolescence.[13] In addition to acute effects and disorders, substance use in children and adolescents can harm the healthy development of the body, brain, and behaviour.[14] Exposure to maternal substance use before birth, environmental tobacco smoke in childhood, or disrupted parenting associated with substance misuse within families have been implicated as early risk factors increasing the odds of subsequent progression to harmful patterns of drug use in adulthood.[15] A recent review found that tobacco use in early adolescence increased the risk of progression in adulthood to tobacco dependence and problems with alcohol and mental health.[16] Brain development, which continues through adolescence, can be placed at risk by use of alcohol[17] and other drugs.[18] These general findings have led to prevention and intervention programmes adopting a range of targets, including reduction of parental substance use, delaying the age of first substance use, and reducing the frequency and amount of substance use in adolescence.[14]

Patterns and trends

Data from clinical populations are clearly inadequate for monitoring population trends in adolescent substance use. Representative household surveys are done in several countries[19–22] and offer the prospect of including young people who are not in school, but have weaknesses such as low response rates and failure to include homeless young people.[20]

In developed nations, universal schooling provides quite comprehensive capture of student populations, offering the potential to monitor early use patterns in younger age groups. Monitoring The Future (MTF) is a well-done student survey done yearly in the USA with large, nationally representative samples.[23] The survey was launched in 1975 and now spans more than 30 years. A European consortium (ESPAD) implemented an adaptation of the MTF survey on three occasions in 1995, 1999, and 2002,[8] enabling comparison of international trends. The MTF has recorded a reduction in many forms of substance use in recent years. For example, the rate of US secondary school students in their final year who reported drinking alcohol in the past month fell from 69% in 1983 to 48% in 2004.[23] The reduction in youth alcohol use in the USA began in the mid 1980s, encouraged by factors such as the 21-years age limit for legal drinking.[24] Reductions have also been mirrored by lower rates of drinking in early high school. Use of tobacco, cannabis, and illicit drugs have also shown general reductions, although from the early 1990s

younger cohorts began to show increases. This recent increase has been explained by so-called generational forgetting, in which younger generations tend to engage in more drug use when they have not directly witnessed the social upheaval of drug use in immediately older generations.[23] The ESPAD surveys have revealed generally higher rates of alcohol and tobacco use for European youth but, in most countries, lower rates of use of cannabis and illicit drugs, compared with the USA.[7] However, average European data mask considerable diversity, with young people in most northern European nations reporting high use of alcohol associated with alcohol-related problems, whereas those in several southern European nations report use of alcohol with few apparent problems, although rates of tobacco and inhalant use are often high in these nations.[7] Patterns in young people in Australia[25] and New Zealand tend to be similar to those in northern Europe. Post-school follow-up of the MTF samples in the USA has been regularly completed, mostly showing stability of patterns from high school into young adulthood, whereas alcohol use tends to increase after leaving school, especially for those entering college.[26]

Intervention conceptual models and frameworks

In 1998 the UN called for a balanced approach to drug policies aimed at reducing both supply and demand.[31] Efforts to reduce supply, primarily through law enforcement punishment for possession and distribution (ie, the War on Drugs), have remained the primary focus in many countries including the USA and UK.[32–34] Other countries, such as Australia, have achieved better balance, implementing supply-reduction strategies designed to disrupt production and supply of illicit drugs, demand-reduction strategies to prevent the initiation of drug use, and harm-reduction strategies to reduce drug-related harm for individuals and communities.[35]

In adolescents and young adults, prevention is a central demand-reduction strategy. Traditional classification of prevention approaches includes primary, secondary, and tertiary strategies. Primary prevention aims to reduce risks and prevent new cases, secondary prevention seeks to limit harm in the early stages of a disorder, and tertiary prevention treats the long-term sequelae and consequences of the disorder. An alternative conceptualisation categorises approaches on the basis of level of risk of a disorder in various groups targeted.[36] Universal interventions are directed at whole populations at average risk; selective interventions target groups at increased average risk, and indicated interventions target individuals with early emerging problems.

Across prevention and treatment approaches, the specification of abstinence as the only acceptable outcome is a key controversy. Among adolescents, zero-tolerance approaches to drug and alcohol prevention are ineffective and in some cases contraindicated.[37–39] With respect to treatment, abstinence-only approaches functionally deny services to those unwilling to completely eliminate use. Consequently, harm-reduction approaches have emerged in recent years to offer alternatives to zero-tolerance. Such approaches acknowledge that many adolescents will at least experiment with substance use, and offer strategies designed to reduce potential consequences of use.[40]

Reductions in pre-birth maternal use of drugs, environmental tobacco smoke, and substance-impaired parenting have been associated with reduced risk of adolescent substance misuse and mental health problems.[41] Unsurprisingly, developmental perspectives have been widely incorporated in attempts to understand and reduce adolescent substance use. Common early social developmental pathways predict a range of psychosocial problems, including problematic involvement with both legal and illegal drugs. Social developmental risk and protective factors originate not only during the early years but also in a range of environments, such as education systems and local communities, and are affected by cultural factors.[42,43] Emerging strategies focus on objectives relevant to positive youth development, such as social participation and wellbeing. The developmental perspective also emphasises individual and contextual factors that

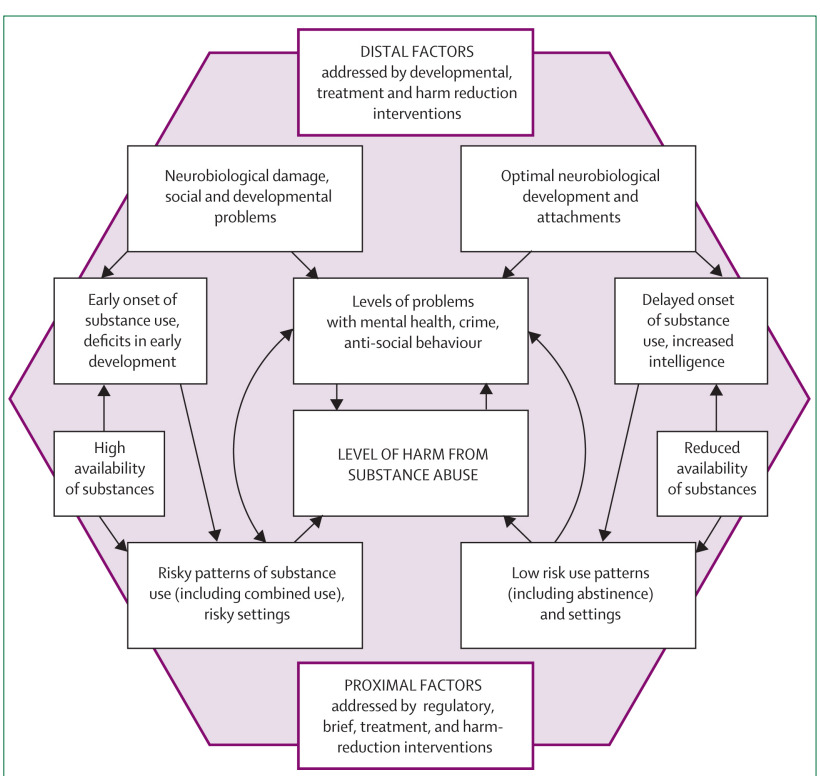

Figure: **Protection and risk model for distal and proximal determinants of risky substance use and related harms**
Adapted from Loxley and colleagues.[44]

contribute to the development of skills that individuals bring to current situations as well as the importance of situational factors, particularly in adolescence (eg, peer interactions). Loxley and colleagues[44] proposed a synthesis between the developmental pathways approach and efforts to reduce drug-related harm at the population level (figure). In this integrated model, risk factors that predispose young people towards harmful drug use range from distal (eg, early developmental, social, and behavioural) to proximal (patterns and places of drug use). The concept of protection was also expanded to incorporate more proximal factors such as harm-reduction programmes, reduced drug availability, and low risk patterns of use (including abstinence).

Differing demand-reduction frameworks and aspects of supply reduction can be related to alternative explanatory models of substance use in young people.[42,45,46] A recent integrative review of published work identified four major motivational processes that affect adolescent substance use: conforming to norms, individuating identity, escaping distress, and self-management and regulation.[46] Conforming to norms includes processes of social influence and legal sanctions. Conformity influences are the most prevalent motivational process affecting adolescent drug use, explaining the common occurrence in most nations of young people conforming to prevalent societal patterns of substance use.[42] In the context of prevalent peer drug use, puberty can trigger drug use motivated by the desire to be popular with peers.[47] Individuating identity describes a less common situation of novel classes of drug use (eg, ecstasy in the 1990s) emerging almost exclusively within youth culture. Liberalisation of female gender roles has been associated with an increase in substance use and harm.[48] The historical emergence of wide-scale recreational use of illicit drugs in the 1960s has been linked to social freedoms stemming from technological mastery and the related pattern of a large proportion of young people delaying adult responsibility to pursue education.[45] The most severe and harmful substance use problems are prevalent in an important minority motivated by escaping distress associated with developmental difficulties occurring from before birth (eg, exposure to alcohol and drug use during pregnancy) and throughout childhood (eg, child abuse and neglect).[15] Longitudinal research suggests that developmental problems are more likely where several risk factors are present, and persist over longer periods of time.[49,50] Finally, a complex range of diverse substance use problems can be traced to pharmacological advances in drug development and the maladaptive replacement of traditional methods of achieving functional benefits such as self-management and regulation (eg, overuse of antibiotics, using tobacco to regulate mood, abuse of analgesics, diet and body-building drugs). Favourable attributions and expectations for the effects of substance use predict intentions to use drugs, which in turn predicts initiation of substance use.[45]

	Processes (populations)	Level of evidence
Regulatory	Using law, policies, and enforcement to reduce supply and demand (universal)	Effectiveness
Developmental prevention	Improving conditions for healthy child and adolescent development (targeted and universal)	Efficacy
Early screening and brief intervention	Brief motivational interventions to reduce high-risk use (targeted)	Efficacy
Treatment	Tertiary prevention of substance use disorders (targeted)	Further evaluation required to establish efficacy
Harm reduction	Reducing harms but not necessarily levels of use (targeted and universal)	Effectiveness for some interventions

Table 3: **Major intervention types and level of evidence**

Evidence for different interventions

In the following sections, we present the major interventions that have evidence for successful reduction of adolescent substance use and related harm. These interventions address different developmental stages and motives for substance use. We assess evidence for supply-reduction (regulatory) interventions, the demand-reduction strategies of developmental prevention intervention, early screening and brief intervention, and treatment and harm-reduction interventions. Table 3 summarises the main conclusions relevant to the level of evidence for each of the interventions described below.

Regulatory interventions

Regulatory interventions to limit drug-related harms can address reduction of supply and motivations for conformity, and range from unfettered access to prohibition with criminal sanctions. Laws controlling substances categorised as narcotics in UN conventions, such as cocaine, heroin, and amphetamine,[51] may receive stringent enforcement with criminal sanctions—even the death penalty in some countries. In some jurisdictions, however, civil penalties (fines) and cautions for first time offenders apply.[10] Regulatory frameworks for legal substances increase the options for influencing health outcomes—eg, controls over who is permitted to supply substances, the user's age or level of intoxication, the hours of sale, quantity permitted, and price.[52]

Controls on price, usually through taxation, are among the interventions with the highest evidence for effectiveness in reducing levels of harm in the population,[52,53] especially for young people.[54–56] Taxes on the alcohol or tobacco content of products (eg, favouring drinks with a lower alcohol content) and indexed for consumer pricing movements[53] are the most effective.

Other strategies with evidence of effectiveness include: ignition interlocks for individuals who repeatedly drive when drunk, enforcement of laws that prohibit service to intoxicated patrons, limits on outlet density, and rationing and restrictions on the hours and days of sale.[52,57] Passive

smoking regulations and their enforcement have had a powerful effect on rates of smoking and related harms.[53] Substantial evidence of effectiveness exists for enforcement of minimum age laws and increasing the age at which young people are permitted to purchase alcohol.[52,58] The use of young people attempting to make illegal purchases to check compliance with minimum age regulations[59] and enforcement of youth possession laws[60] are procedures that contribute to efficacy. Regulatory strategies to minimise the availability of inhalants are worthy of evaluation to establish efficacy—eg, providing aviation fuel for cars in remote rural areas of Australia to prevent young Aboriginals from petrol sniffing.[61]

The enforcement of laws on youth access, passive smoking, and licensing of alcohol can often be determined locally. In recent years, controlled trials in which communities were encouraged to enforce these laws have yielded evidence of effectiveness in reducing alcohol-related violence and road crashes,[62] especially if supported by increased taxes.[63]

Regulatory changes regarding illicit drugs and illicitly available prescription drugs that are worthy of evaluation to establish efficacy include: the prescription of heroin to severely dependent individuals, monitoring the use of multiple family doctors by the same individual to obtain psychotropic medication, and modification of legal sanctions from criminal toward civil penalties.[53]

Developmental prevention interventions

Developmental prevention interventions aim to reduce pathways to drug-related harm by improving conditions for healthy development in the earliest years through to adolescence. The interventions beginning before birth aim to reduce drug use motivated by escape from distress, by reducing risk factors such as use of tobacco, alcohol, or other drugs in pregnancy and exposure of children to environmental tobacco smoke. There is evidence of efficacy from small well-controlled trials that family home visitation is a feasible strategy for implementation with disadvantaged families and can reduce risk factors for early developmental deficits and thereby improve childhood development outcomes.[64] Follow-up at age 15 years has associated such interventions with reduced rates of early initiated tobacco and alcohol use.[41] In the USA, savings and returns to government have been estimated across a range of areas at around US$5 for every $1 spent on the programme over the first 15 years of the child's life. This strategy might not demonstrate benefits where it is applied more universally to include mothers who have low rates of child development problems.[65] The Perry Preschool programme has encouraged intensive early preschool experiences combined with home visits for families targeted because of high rates of child development problems.[66] A small experimental trial of this programme followed up children until age 27 years and found developmental advantages, including lower rates of substance use,[66] with aggregated benefits translating to a US$6 saving for every $1 invested.[65] The effect of early developmental disadvantage on progression to harmful substance use is not inevitable but can be moderated by reducing its translation to social marginalisation. Some of the strongest evidence for efficacy in reducing developmental pathways to drug-related harm comes from interventions delivered through the early school years to improve educational environments and reduce social exclusion.[67,68] A recent independent economic evaluation estimated that savings on overall social and health costs were large, at US$9837 per student through effective intervention in the early school years.[69]

Many interventions targeting the high-school age period focus on reduction of motivations for drug use related to conformity, individuating, and self-management. Drug education in schools has been the most commonly evaluated strategy. Components of the curriculum that address social influences on drug use aim to develop young peoples' competence to resist peer pressure.[70] Drug education based on social competence training has shown efficacy in delaying drug use by about 1 year.[71] These approaches address conformity and individuation pathways and can be combined with information to reduce perceived prevalence. Drug education programmes addressing emotional competence include stress management components to improve the individual's ability to cope effectively in difficult situations. Reviews typically show that information is insufficient on its own to prevent initiation of substance use.[70] More recent schemes have incorporated harm-reduction information, and evidence from an Australian trial shows reductions in alcohol use and misuse after 2 years.[72] Encouraging efficacy evidence suggests that reductions in alcohol[73] and tobacco use[74] are achievable through interventions to alter norms and consequences for drug use within families through the early adolescent years. In general, prevention programmes seem more successful when they maintain intervention activities over several years and incorporate more than one strategy. Developmental prevention programmes are unlikely to be adequate as a stand-alone policy to reduce population harm related to substance use, particularly for substances such as tobacco where the burden of harm falls late in life.[75] However, opportunities exist for communities to tailor a mixture of programmes that address the local conditions that give rise to substance-related harm, and developmental prevention schemes can be usefully coordinated with regulatory approaches and with treatment and harm-reduction programmes. Developmental prevention activities can be coordinated using funding from different jurisdictions—eg, crime prevention, health promotion, mental health, education, and substance abuse prevention.[14]

Early screening and brief intervention

Findings of longitudinal cohort studies in different nations show that use of a specific substance early in life increases the risk of progression to more frequent and problematic use in later life.[14,76] However, the trend for early substance use to predict later problems masks considerable variation, and programmes based on principles of harm reduction have demonstrated success in encouraging young alcohol users to adopt more moderate and less harmful patterns of use.[77] One feasible intervention framework that has efficacy evidence combines early screening of adolescent substance use behaviour and brief interventions aimed at encouraging behaviour change. Brief motivational enhancement interventions using motivational interviewing principles have shown substantial promise and have been widely implemented to address use of alcohol, tobacco, and other drugs.[78,79]

Many adolescents who drink heavily or use other drugs tend to grow out of their addictive behaviour pattern as they enter adulthood,[80] opening opportunities for encouraging this process through assessment centred on health risks and consequences associated with current patterns of use. A useful screening assessment measure for alcohol problems is the Rutgers Alcohol Problem Index (RAPI),[81] which includes questions designed to assess consequences of problems (such as hangovers, cognitive impairment, and interpersonal conflict).

The stages of change model[82] has been used to guide brief intervention strategies. Initially developed to describe the stages people progress through in smoking cessation, this model has since proved influential in guiding treatment for a range of addictive behaviours. Although the model has provided an influential heuristic model, evaluations to date have not supported its use in improving treatment outcomes.[83]

Motivational interviewing, developed by Miller and Rollnick,[84] is a patient-centered interviewing style with the goal of resolving conflicts regarding the pros and cons of change, enhancing motivation, and encouraging positive changes in behaviour. The interviewer style is characterised by empathy and acceptance, with an avoidance of direct confrontation. Any statements associated with positive behaviour change that the patient brings up in the discussion are encouraged so as to support self-efficacy and a commitment to take action. Motivational interviewing and other interventions that focus on resolving ambivalence (eg, evaluating the pros and cons of change versus no change) might increase intrinsic motivation by allowing patients to explore their own values and how they may differ from actual behavioral choices (eg, "I want to be a good student, but I often spend my daytime hours hung-over and my evening hours getting drunk"). A meta-analysis of 30 clinical trials of motivational interviewing showed that the technique is more effective than no treatment or placebo controls, and as effective as other active treatments for alcohol and drug problems, diet, and exercise.[85] Motivational interviewing has also been successfully adapted and applied with a range of other health behaviours, including use of illicit substances,[86,87] smoking,[88] and HIV risk reduction.[89]

The motivational interviewing approach, as used in the Brief Alcohol Screening in College Students (BASICS) programme, has been effective in reducing binge drinking and excessive drinking in college students.[90] This brief intervention consists of two one-on-one interviews designed to promote reduced alcohol consumption or abstinence among high-risk drinkers. The format is guided by personalised feedback, including descriptive graphs presenting the patient's own drinking patterns relative to normative trends, negative consequences of drinking, and related attitudes and beliefs. An attempt is made to resolve ambivalence about changing one's drinking behaviour and a move toward a safer drinking plan. BASICS is efficacious in reduction of alcohol use and associated drinking problems in several long-term follow-up studies,[91,92] and has been selected as a model programme in the USA.

Another setting in which brief interventions are effective is in primary and specialty medical care settings. Training doctors to communicate with adolescents has been shown to increase rapport and trust.[93] A brief session (5–10 minutes) of advice from a doctor that is directed toward the risks of excessive consumption and strategies to avoid excessive drinking can significantly reduce alcohol use.[94–97] In developing prevention programmes, the adolescent patient's risk and protective profile is important to consider[97,98] in planning topics to be covered. Brief interventions have also been shown to be effective in working with patients who are treated in emergency room settings[100] or trauma centres[101] where alcohol or other drug use may have been involved. Other evidence suggests that brief interventions can be feasible for young cannabis users[102] and effective in reduction or elimination of tobacco use and other illicit drug use in adolescent patients.[78,79,103] The challenge remains as to how to provide the training and financial incentives to make screening and brief interventions for problem substance use routinely implemented across health-care systems.[104]

Treatment

Systematic reviews show inconsistent outcomes after treatment for substance-use disorders in adolescence[105] and current practice fails to implement the most promising approaches.[106] Issues that complicate the treatment of adolescent substance abuse and dependence include inadequate screening, assessment, and access to care.[106,107] Traditional evidence-based approaches for treatment include cognitive-behavioural therapy, contingency management, family-based therapy, and

12-step programmes.[108] In general, psychosocial treatment is better than no treatment, but much more research is needed to evaluate which approaches work better for which individuals.[108] There are potential risks of escalating problems where treatment programmes aggregate young people with antisocial behaviour.[109,110]

Relative to psychosocial therapy, pharmacotherapies for adolescents have been less frequently evaluated. Few studies have evaluated pharmacotherapies specifically designed to treat substance use.[111] Approved medications for treatment of addiction to alcohol (eg, disulfiram, naltrexone, acamprosate), opiates (eg, methadone and buprenorphine), and nicotine (bupropion, nicotine replacement)[112] may or may not be appropriate for adolescents. In the absence of empirical evidence documenting efficacy of pharmacological treatments for adolescents, caution is warranted in use of treatments for which evidence supports use in adults. Some evidence supports the use of naltrexone in the treatment of adolescent alcohol dependence.[113] Nicotine replacement and bupropion have shown modest effects in treating nicotine dependence but are not contraindicated in adolescents.[114] Substitution medications, particularly for opiate treatment, are generally appropriate only for individuals with long histories of use, severe use, or both and are likely to be less appropriate in younger than in older adolescents. To date, no systematic research has been done for pharmacotherapies targeting opiate dependence in adolescents. Moreover, existing evidence for these and other treatments are underwhelming and larger controlled trials are needed.[111]

Recent evidence suggests about 60% of adolescents with substance use problems also have one or more co-occurring disorders,[115] the most common of which include conduct disorder, oppositional defiant disorder, and depression. Other common psychiatric conditions include anxiety disorders and attention-deficit hyperactivity disorder (ADHD).[115] Adolescent substance users with comorbid disorders generally report greater severity of symptoms and respond less well to treatment than do those without comorbid disorders.[116] By contrast with pharmacological treatments that specifically target substance use in adolescents, better evidence has been established for pharmacological treatment of co-occurring conditions. Successful pharmacological treatment of co-occurring conditions, particularly affective disorders, is typically associated with reduced substance use problems.[108,111]

Reasonable efficacy evidence exists for treatment of illicit drug use in older adolescent populations (eg, age 17–24 years). Methods that involve some drug substitution (eg, methadone or buprenorphene) showed strong evidence of improved social functioning, health, and treatment compliance.[117] Promising evidence also exists of improved outcomes with prescription of heroin to people with opioid dependence.[118] Further research is needed on these modalities specifically for adolescent populations.

Non-medical use of prescription medications, particularly opioid analgesics, has become a rising problem among adolescents and young adults.[119] In the USA, in 2004, 10·5% of 12th graders reported past year non-medical use of Vicodin (hydrocodone and paracetamol) and 4·5% reported past year use of oxycodone.[23] Other prescription drugs that are quite frequently used illicitly, especially in young adult college students, include stimulants, anxiolytics or sedatives, and sleeping medications. Peers are the most commonly reported source of these substances.[120] In adolescents, methylphenidate and dexamphetamine are widely prescribed in the treatment of ADHD. The availability of ADHD drugs combined with their classification of high abuse potential has inspired concern that has not, at least to date, been justified, since prevalence of abuse is quite low.[121]

Harm reduction

In most communities, a substantial minority of adolescents show heavy and harmful patterns of illicit drug use that seem to be motivated by escaping distress and that are difficult to change. Harm-reduction interventions (table 4) attempt to prevent problems by

	Risk patterns	Main populations	Prevalence of harm	Recommended harm-reduction interventions
Tobacco	Regular use and dependence	Universal	Leading cause of drug-related harm overall	Restrictions on environmental tobacco smoke in public places*, smoke-free alternatives†
Alcohol	Intoxication and regular use	Universal, male individuals	Second leading cause of harm, first in some regions	Random breath testing of drivers*, safe glassware†, thiamine-fortification of drinks and flour*
Cannabis	Regular use and dependence	Universal, male individuals	Low for health-related harms, high for criminal justice costs	Use of civil penalties to reduce social harms with criminal penalties*
Other illicit substances	Overdose, intoxication, dependence	Socially and developmentally disadvantaged, male individuals	Lower than legal drugs for health and social costs, high for law enforcement costs	Needle exchanges*, hepatititis B vaccination for users*, prescribed heroin‡, safe injecting rooms†
All substances	Intoxication, regular use, dependence	Universal, young people, male individuals, disadvantaged	Substantial (see tables 1 and 2)	Public education about the care of intoxicated persons at risk of fatal overdose†

Level of evidence: *Effectiveness. †Evidence for feasibility but requires research for efficacy. ‡Efficacy.

Table 4: **Overview of recommended patterns of harm-reduction investment by type of substance**[57]

targeting risky contexts or patterns of use, or by moderating the relation between use and problem outcomes, without necessarily affecting overall rates of use. The available evidence supports harm reduction approaches as an effective strategy that can save lives and reduce harm amongst adolescent alcohol and drug users, with effects measurable at a population level. Harm-reduction strategies including random breath testing and graduated driver licensing have effectiveness evidence that they can reduce vehicle accidents and related death and injury.[59] Improved enforcement of drink-driving laws has been linked to reductions in youth suicide and risky sexual behaviour.[122,123] Environmental enhancement strategies, such as serving alcohol in shatter-resistant glasses, face little political opposition while reducing alcohol-related injuries.[53] A wide body of research supports the view that needle and syringe exchange programmes have been effective in preventing HIV infection, without encouraging any increase in drug use.[53,124,125] Targeted health interventions such as hepatitis B vaccination can reduce the risk of disease transmission through injecting drug use.

Research limitations and prospects

The development, evaluation, and implementation of interventions is dependent on social and political support. The availability of data is therefore affected by culture and context. The expense entailed in evaluation has largely limited published work to high-income countries (North America, Australasia, and Europe). Adolescent substance use is expected to become an increasing burden for developing countries in future.[3] Emerging practices, such as globalisation in substance marketing[126] and the increasing penetration of tobacco products into developing countries,[127,128] might require a specific-focus for intervention and evaluation in coming years.

Conclusions

Substance use, especially heavy use of alcohol and illicit drugs, contributes substantially to the burden of disease in adolescents. Evidence suggests that rates of tobacco use, harmful alcohol use, and illicit drug use in young people can be reduced through the concerted application of a combination of regulatory, early-intervention, and harm-reduction approaches. Reviews have called for a more concerted effort to address harms associated with youth alcohol use through regulatory strategies and improved dissemination of brief intervention approaches.[57] Long-term opportunities exist to reduce pathways to severe patterns of illicit drug use with early developmental prevention frameworks. Although harm-reduction approaches such as needle exchange programmes often face political controversy, they have a strong evidence base as interventions that contribute to saving lives and reducing disease in disadvantaged populations. Medical practitioners, together with other health professionals, have a responsibility to seek balanced policy by advocating for and practicing the best evaluated health interventions. Although great progress has been made over the past 3 decades, many interventions still only have evidence of efficacy, and need to be evaluated in real-world settings to establish effectiveness.[57]

Conflict of interest statement

We declare that we have no conflict of interest.

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Reversal of coma with an injection of glue

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In June, 2006, a 68-year-old man was transferred to our hospital in a coma. He had a 2-day history of new-onset generalised headache followed by a decrease in his level of consciousness. He was on warfarin for atrial fibrillation. There was no history of trauma.

On examination, the Glasgow coma scale score was 7 (E1 M4 V2) and there were bilateral Babinski signs. CT showed bilateral acute-on-chronic subdural haematomas (figure A). Laboratory test results showed a prolonged prothrombin time of 27·3 s (normal 10·6–14·0) and an INR of 2·4 (normal 0·8–1·3). We administered fresh frozen plasma. On further questioning, the patient's wife revealed that his headache had been exquisitely positional, occurring only when he was upright and resolving completely within 1–2 min when he lay down. MRI confirmed the clinical suspicion of spontaneous intracranial hypotension: it showed sagging of the brain, enhancement of the pachymeninges, and subdural fluid collections (figure B). The patient was placed in the Trendelenburg position at a 45° angle, following which his level of consciousness improved rapidly (Glasgow coma scale score 14 [E4 M6 V4]). CT myelography showed an opening pressure of 3 cm water (normal 6·5–19·5) and a thoracic meningeal diverticulum associated with a cerebrospinal fluid (CSF) leak. The patient received a lumbar epidural blood patch of 50 mL autologous blood. The patient then regained full consciousness for about 48 h, after which he deteriorated with a widely fluctuating level of consciousness, his Glasgow coma scale scores varying between 6 and 14 depending on his position. 2 mL fibrin glue (Tisseel, Baxter BioScience, Westlake Village, CA, USA) was administered percutaneously through an 18 gauge needle at the site of the CSF leak. The next day, the patient was able to walk; he had a normal sensorium and no headache. An MRI scan showed that the brain was sagging less and the subdural haematomas were smaller; the pachymeninges were no longer enhanced. When last seen at follow-up in January, 2007, the patient was well.

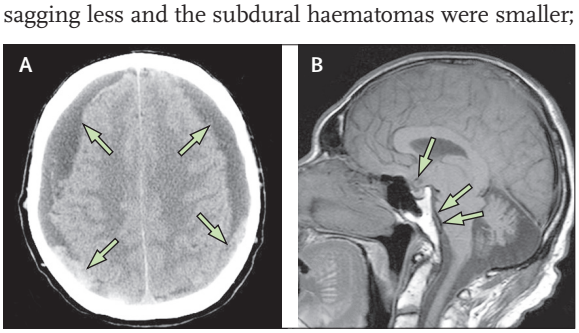

Figure: **Pretreatment imaging studies**
(A) CT shows bilateral acute-on-chronic subdural haematomas (arrows). (B) Sagittal T1-weighted MRI shows sagging of the brain with downward herniation of the optic apparatus (arrow) into the sella and flattening of the pons (arrows).

Spontaneous intracranial hypotension is caused by a spontaneous spinal CSF leak and is an important cause of new headaches in young and middle-aged adults.[1] Mechanical factors combine with an underlying connective-tissue disorder to produce the CSF leak.[1] Spontaneous intracranial hypotension is not rare, but it is frequently misdiagnosed.[1] A positional headache is the prototypical symptom but other headache patterns occur as well. Various associated clinical manifestations have been reported, including coma: which, in this case, was caused by severe sagging of the brain leading to diencephalic deformation.[2–4] Subdural haematomas are found in about 20% of cases.[5] The typical MRI findings are subdural fluid collections, enhancement of the pachymeninges, engorgement of venous structures, pituitary hyperaemia, and sagging of the brain (mnemonic, SEEPS).[1] Treatments should be directed at the CSF leak. They include—in order of invasiveness—bed rest, epidural blood patching, percutaneous injection of fibrin glue, and surgical repair.[1] Although subdural haematomas can appear quite ominous, with a significant mass effect, their primary treatment is rarely indicated.[5] Indeed, evacuation of subdural haematomas in the setting of spontaneous intracranial hypotension is associated with a high risk of worsening or recurrence of the subdural haematomas if the CSF leak is left untreated.[5] Careful history-taking is therefore required when patients present with new-onset headaches and coma. In this case, the subdural haematomas could easily have been attributed solely to the warfarin use, even in the absence of any trauma; the coma could have been attributed (incorrectly) to the subdural haematomas: but the positional feature of the headaches suggested the diagnosis of spontaneous intracranial hypotension.

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