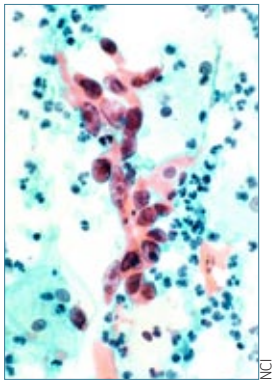
Cervical intraepithelial neoplasia and higher long term risk of cancer

Women treated for CIN3 should have long term regular screening, even if they are beyond the normal age limit



NCI

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In some countries, such as the United Kingdom, women have long term intensive surveillance after conservative treatment for high grade cervical intraepithelial neoplasia, whereas in others, such as the Netherlands and Finland, they return to regular screening after a few years. The second choice is based on the consistent observation that most recurrences of cervical intraepithelial neoplasia occur in the first two to three years after treatment.[1]

In this week's *BMJ*, Strander and colleagues provide strong evidence that women treated for cervical intraepithelial neoplasia grade 3 have a long lasting excess risk of invasive cervical cancer.[2] Among more than 130 000 women with this condition, the age adjusted incidence was more than double that of the general population up to 20-25 years after diagnosis. The excess incidence was greater in women treated at older age and in recent years.

How do these findings translate into clinical recommendations? The important question is how different follow-up schedules compare in terms of effectiveness and cost in preventing the excess risk of cancer. Unfortunately, we have no direct evidence to answer this question, as no large study of the risk of cancer has also reported women's individual follow-up history.[2-4]

Long term surveillance with intensive cytology might be an option. However, the relative protection afforded by different frequencies of testing in the general population[5] cannot be assumed to be the same for women treated for high grade cervical lesions. Indeed, without data on individual follow-up the long term excess risk of cancer may be explained by cytology becoming less accurate in the long term in treated women or by women not attending long term intensive follow-up or even regular screening.[1] It would take a long time for prospective studies of women with different follow-up regimens to identify the most effective regimen. Case-control studies comparing the follow-up of women who developed cancer with those who did not might provide crucial information in the short term. The interval since the last normal cytology result is the key variable, and studying the risk of cancer according to this interval and time since treatment might identify the best regimen.

Testing for human papillomavirus DNA has consistently been shown to be more sensitive than cytology for detecting short term occurrence of cervical intraepithelial neoplasia in treated women.[6] Long term schedules need to be defined. Repeated testing for human papillomavirus may be needed to control the long term risk of cancer, because residual infection might be difficult to detect and new infection needs to be identified. Increased risk of cancer could be the result of a new or persistent infection rather than treatment failure. Women who were previously infected could still have the same risk factors such as behaviour or susceptibility to infection. The high negative predictive value of human papillomavirus means that women could be tested less often compared with cytology. The scarce data available on follow-up by colposcopy do not show a substantial advantage over cytology.[7]

One clear indication is that women treated for cervical intraepithelial neoplasia stage 3 should continue surveillance beyond the age limit of regular screening. Such age limits have been adopted for the general population as cancer risk drops to negligible values in previously regularly screened women, but Strander's study[2] shows that this is not the case in women who had cervical intraepithelial neoplasia stage 3.

According to Strander's data,[2] any follow-up policy that can confer the same cancer risk as that seen in the general population would avoid 21.5 cancers per 100 000 person-years (including an unknown but possibly large proportion of microinvasive carcinomas) in these high risk women. Related disadvantages are not only financial but include stress related to long term intensive surveillance and the risk of having to be retreated unnecessarily as a result of false positive histology. Increased frequency of testing will lead to an increased number of biopsies and, in the general population, about 15% of diagnoses of cervical intraepithelial neoplasia grades 2-3 are not confirmed at review.[8]

The higher incidence of recurrence of cervical neoplasia in women treated in recent years correlates with the use of more conservative treatments. As for all ecological correlations, alternative explanations are difficult to exclude. For example, the higher prevalence of human papillomavirus in recent years might have made persistent hazardous sexual behaviour increasingly risky. Again, comparing by calendar period the type and characteristics of treatment (for example, if excision margins were free of dysplasia) in women who did and did not

develop cancer would provide precious information.

In the meantime, returning to the widespread use of hysterectomy for cervical intraepithelial neoplasia is clearly unacceptable, especially as only some high grade cervical lesions progress to cancer[9] and the incidence of false positive histological diagnosis is relatively high.[8] Regarding excision, no significant difference in obstetric outcomes has been shown between cold knife conisation and other excisional techniques,[10] although short term complications were more frequent with cold knife conisation.[11]

Current evidence calls for high quality conservative treatment—this might be more achievable in centres with a high workload volume. In addition, more attention should be paid to the completeness of excision, especially in older women who have a higher risk of cancer.

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Child wellbeing and inequalities in rich countries

Evidence needed on how best to reduce inequalities

RESEARCH, p 1080

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A recent Unicef report ranked the wellbeing of children in 21 rich countries.[1] The report aggregated national data on more than 40 indicators from credible sources in six dimensions—material wellbeing (related to income, poverty, material goods), health and safety, educational wellbeing, family and peer relationships, behaviours and risks, and subjective wellbeing (how the child sees his or her self). The press had a field day when the report was published,[2] because the United States and the United Kingdom were in the bottom five countries for five of the dimensions. The UK ranked 12th in health and the US ranked 12th in education; questions were rightly asked about how this could happen and what the government was going to do about it.

In this week's *BMJ*, Pickett and Wilkinson[3] attempt to explain the results of the Unicef report by combining the measures of wellbeing of children with national data on income. They selected three measures of income—income inequality (ratio of the top fifth of incomes to the lowest fifth); relative child poverty (the proportion of children living in households in which the income was less than 50% of the national median); and average income (gross national income per capita in 1999). Rather than taking national aggregates, with all types of children grouped together, the authors disaggregated the data; this approach revealed the profound impact of poverty—lower scores of wellbeing were seen right across the board for children in the lowest income groups.

Wellbeing—the state of being happy, healthy, and prosperous—comprises more than just health. Measuring health in the simplest sense, by measuring mortality and morbidity, falls short of what is needed to measure wellbeing. Measuring material poverty is simply not enough to measure inequality. As a result, measurements of both wellbeing and inequality have evolved rapidly in the past 10 years.

Several data sources are used to measure the health of children, but few take into account the many contexts in which children grow and develop, including their family and community environments. Databases that do this are relatively new—for example, the US national survey of children's health—which started in 2003.[4] The Unicef report represents a welcome progression towards more complex tools that compile primary and secondary data to measure composite indexes of health and wellbeing. It adds depth and data to our understanding of what our children experience and confirms what we already know—that even the richest countries have poor children, and that these children do not fare so well on many counts.

Measures within populations or groups of people identify the differences and inequalities that occur, but they do not explain why they occur or recommend how they could be changed. Picket and Wilkinson's study goes some way to dealing with these matters by disaggregating data on wellbeing into their separate constituents and combining them with national data on incomes. The implications of the results on policy are clear—we must invest more money in children, especially those at the bottom of the pile. We have opportunities to affect development in childhood that will never occur again. The difficult question is—what kinds of investment work?

One suggested framework is a coordinated and

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integrated country-wide response that makes evidence based changes in social and economic policies; improves living and working conditions; and strengthens the health of communities and individuals, via social networks and effective healthcare interventions.[5] A systematic review of health interventions that reduce inequalities recommended a framework comprising the systematic, intensive delivery of effective health care and improved access to health services, together with reminders to use these services. This should be achieved by a multidisciplinary approach, which ensures that needs are dealt with and peers are involved in the delivery of interventions.[6]

We may need to invest even before the child is born and to monitor outcomes for years. This makes practical sense, but it is a major challenge to prove that investment before birth is beneficial. Take the case of programmes of home visits by nurses to disadvantaged mothers during pregnancy and two years after birth. A large randomised controlled trial compared the effects of nurses visiting unmarried mothers of low socioeconomic status in New York State with standard care. In adolescence, the children in the intervention group had significantly less serious antisocial behaviour and use of drugs and alcohol.[7] In contrast, a systematic review of similar interventions in the US (five studies) and Australia (one study) for mothers with alcohol or drug problems found no effect on meaningful health outcomes in the mother or child but the studies were limited in quality and in the outcomes measured.[8] Systematic reviews of other home visiting programmes by a nurse or professionally supervised lay person that target disadvantaged teenage mothers have provided limited evidence of a positive effect on quality of parenting and child development outcomes[9]; other reviews, however, have found that parenting programmes targeted at teenage parents resulted in improved psychosocial outcomes for the parent and child.[10] Another review found that parenting programmes delivered to disadvantaged adult mothers showed no evidence of benefit,[11] but this lack of effect may have resulted from a failure to assess the mothers' needs and provide tailored interventions.

Regardless of the inconsistent evidence, we know enough to say that inequalities affect child wellbeing and that poverty kills as effectively as any disease. We need to get better at identifying the programmes that work and much better at getting governments to invest in the wellbeing of children. The debate will hot up in 2008, when the World Health Organization Commission on the Social Determinants of Health will report.[12]

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Defining a high performance healthcare organisation

Composite measures of performance are insufficient on their own

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Why are high performing healthcare organisations so hard to find? In this week's *BMJ*, Wilson and colleagues report a study that evaluates 69 facilities in 30 US states that receive categorical funding for HIV services.[1] The authors assessed performance using a bundle of eight clinical measures considered by a panel of experts to represent high quality of care for HIV. They found that few organisations scored highly across more than a handful of measures.

Interpreting the results at face value suggests that these facilities are not performing well, and that their organisations do not support strong systems of care for people living with HIV. We would expect all clinics to provide comprehensive elements of care that have been shown to improve patients' outcomes. However, closer scrutiny of the study raises methodological and theoretical questions about the selection and measurement of the indicators and, importantly, the association between overall performance and designation as a high performing healthcare organisation.

Composite measures are commonly used to monitor performance in healthcare systems. An overall score is computed by aggregating each component into a bundle of related measures. Bundled measures, however, are not all alike. Selecting measures appropriate to the system under review and defining those measures consistently is crucial to generating meaningful performance data.[2] As Nolan and Berwick[3] point out, some groups of measures are linked because they constitute a sequence of essential steps

leading to one desired outcome, such as an infection control procedure, and omission of one measure compromises the outcome. Other bundles are related to disease; these bundles include appropriate monitoring, treatment, and preventive screening indicators that may need a broad range of strategies to implement within one system of care.

Although the bundle used in Wilson and colleagues' study comprised measures of comprehensive ambulatory care for HIV, they reflect a different type of complexity. Four measures—prescription of highly active antiretroviral therapy (HAART), prophylaxis against *Pneumocystis carinii*, screening for hepatitis C, and flu vaccination—require a provider to follow recommended guidelines. Three other measures—screening for cervical cancer, screening for tuberculosis, and suppression of viral load—are partly dependent on the patients' behaviour and might not yield a reliable picture of organisational quality.

Suppression of viral load is a particularly difficult outcome to interpret as several variables determine the likelihood of response. In some people, suppression never occurs because of resistance to antiretroviral agents; others recently started on HAART might not yet show suppression despite responding to treatment. More importantly, some people do not show suppression because they do not adhere to their regimen.

Although these measures form an ideal package, they are affected not only by the behaviour of the provider, but also by delivery of services, the structure of the organisation, and the behaviour of patients. Ideally, high quality care provided by a model system would consistently perform the activities associated with all these measures; in truth, this rarely occurs. Even if all measures are satisfied during one time period they are not likely to be sustained over time.[4]

High performing organisations are characterised by sustainable performance over time. As complex and dynamic units, organisations face staff turnover, changing leadership, and the effects of external factors. They have unique cultures that influence the quality and sustainability of performance.

Studies of high performing organisations[5-9] find that a good infrastructure is crucial for sustained high performance. Infrastructure unifies important organisational elements, including meaningful strategy and inspired vision implemented by a consistent leadership, a commitment to meeting the expectations of consumers, a dedicated structure for quality, and constant feedback to staff.[7 8] Moreover, attaining the highest levels of performance is not an overnight effort. Time is needed for whole system transformation that includes changing culture, redesigning processes, and crafting solid information systems that support useful and robust measurement, while keeping the vision of quality in sight at all times. Once this transformation is complete, appropriate measures of performance should consistently reflect improved outcomes.

A comprehensive package is necessary to measure system-wide performance, but a one time measurement is clearly not sufficient. Performance must be measured over time to identify whether quality, once achieved, is sustained. In addition, models of organisational clinical performance and frameworks for quality assessment must be united to help us understand the attributes of healthcare organisations that perform well. Frameworks such as the Malcolm Baldridge quality award criteria and the European Foundation quality management excellence model[10] offer a starting point to link organisational variables to clinical outcomes. We have much to learn about how these models intersect, and we need a better understanding of the relation between structural elements and clinical performance. The paradigms of effectiveness research, the psychology of planned social change, organisational theory, and social anthropology may contribute to our understanding of dynamic and complex organisations.[11] Identifying essential attributes of high performing organisations and disseminating strategies for improvement will help us to achieve consistent performance of the highest quality to benefit the general population.

What then is a high performing organisation? Even without looking at performance data, high performance is often apparent when visiting an organisation—performance data are openly displayed on the walls, staff are familiar with their performance, and they openly share ideas for improvement. Evidence of patient input and a commitment to meeting consumer expectations confirm that an organisation is performing well. When the organisational elements supporting sustainable high performance are in place, measurement across appropriate elements is bound to reflect improvement; while performance rates may not all be in the top quarter, they may well be when measured the next time.

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Rate control in permanent atrial fibrillation

Guidelines on the use of digoxin are inconsistent with evidence from randomised trials

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Atrial fibrillation is the most common cardiac arrhythmia and it causes substantial morbidity, especially in elderly people. In June 2006, the UK National Institute for Health and Clinical Excellence (NICE) published new guidelines for control of heart rate in people with chronic atrial fibrillation.[1] The guidelines depart from historical practice by recommending that instead of digoxin, β adrenoceptor blockers or rate limiting calcium antagonists should be the preferred initial monotherapy, except in predominantly sedentary people. Similarly, the revised 2006 joint American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines recommend the use of β blockers or calcium antagonists alone to control heart rate.[2] We have reviewed the evidence to support this fundamental change in practice and challenge its safety.

No single definition of ideal control of heart rate in chronic atrial fibrillation exists.[3] Rate control drugs aim to reduce heart rate at rest and during exercise, without causing excessive nocturnal bradycardia. The ultimate aim of treatment is to improve symptoms and exercise tolerance, and to prevent cardiomyopathy induced by tachycardia. To reduce morbidity, the benefits of treatment need to be weighed against the harms. A substudy of the atrial fibrillation follow-up investigation of rhythm management (AFFIRM) study found no association between achieved ventricular rate and overall survival or quality of life.[4]

Epidemiological studies in the United Kingdom and the United States have reported an overall decline in the use of digoxin, perhaps as a result of recent recommendations. People with atrial fibrillation sometimes take β blockers or calcium antagonists for indications other than arrhythmia. In a descriptive study of the management of rate control in 2027 people, the AFFIRM investigators reported no significant difference in adequate control of heart rate at rest and exercise in people treated with β blockers alone or digoxin alone, which suggests that digoxin is still one of the first line drugs for the management of heart rate.[5]

Of previously published systematic reviews,[6 7] one highlighted the lack of evidence on optimal control of heart rate in people with atrial fibrillation and the importance of symptom control. In the other, the comparisons of β blockers and calcium antagonists with placebo were confounded by most patients on either treatment arm also being on digoxin.[6] Clearly, larger randomised trials are needed to inform prescribing decisions. However, the current evidence on which recommendations have been made is summarised below.

We searched the literature using the Medline, PubMed, and Cochrane databases for studies published in English. By reviewing bibliographies of relevant articles we identified additional studies. We reviewed 57 studies, including 25 randomised double blind controlled trials, assessing digoxin, β blockers, calcium antagonists, and combinations for rate control in chronic atrial fibrillation. The smallest trial recruited six participants and the largest included 136. Differences in methodology and outcomes make direct comparisons difficult. Only a minority of studies reported symptom scores and patient preferences.

Digoxin has long been used for control of heart rate in chronic atrial fibrillation. It acts primarily by exerting a vagomimetic influence on the atrioventricular node and has a positive inotropic effect. It has few side effects but has a flat dose-response curve and a narrow therapeutic index, so that subtherapeutic doses are often used. It is less effective at controlling heart rate during exercise and in states of increased sympathetic activation.

In people with atrial fibrillation, β adrenoceptor blockers have heterogeneous effects on heart rate, depending on their specificity for the β receptor and how much concomitant β agonist activity they possess. Ten studies[8-17] evaluated β blockers alone. The β blocker was better than digoxin in controlling heart rate at rest in only one study,[8] although it improved heart rate during exercise in four studies.[8 9 11 15] Xamoterol (discontinued in the United Kingdom in 2000) was the only β blocker to improve exercise tolerance compared with digoxin, but at the expense of worsening control of heart rate.[13] In six other studies, exercise capacity did not improve when β blockers were used alone. In comparison, several studies have shown that better heart rate control at rest and during exercise is achieved with combined digoxin and a β blocker than with digoxin alone.[8 14 18-28] However, the effect of this combination on exercise tolerance is not consistent—some studies reported deterioration in exercise capacity,[18 19 21 23 28] some reported improvement,[13 22 24] and others reported no change.[14 15 18 20 25 27 29] Other side effects were reported with the use of β blockers in the above studies and, importantly, two studies reported worsening symptoms of heart failure on withdrawal of digoxin in people with heart failure.[13 14]

The calcium channel blocker diltiazem has been evaluated in five studies.[15 30-33] They found that diltiazem was better than digoxin at controlling heart rate during exercise, but not during rest, and no improvement was seen in exercise capacity. Eleven studies[15 21 22 30 32-38] assessed the combination of diltiazem and digoxin; most of these reported improved heart rate control at rest and exercise when compared with digoxin alone. Two also found improved exercise tolerance with the combination.[22 36] One person developed worsening heart failure

after discontinuation of digoxin while receiving diltiazem 360 mg daily.[33] In another study, two people with previous episodes of heart failure deteriorated when digoxin was discontinued.[30]

Results were similar when monotherapy with verapamil was compared with digoxin. Verapamil improved heart rate during exercise compared with digoxin in three studies.[31 39 40] Exercise tolerance with verapamil alone improved in two of the three studies that tested it.[17 40] The combination of digoxin with verapamil provided better heart rate control at rest and during exercise than digoxin alone.[20 18 36 41-46] However, bradycardic episodes or pauses were sometimes seen with the combination. Exercise tolerance was not consistently improved despite better heart rate control, with some studies reporting improvement[36 40 41] and others no change.[18 20 44 47] Concomitant use of both drugs increases digoxin concentrations.

Limitations to the use of verapamil and diltiazem include their negative inotropic effects and considerable dose related side effects.

In patients with chronic atrial fibrillation, digoxin has been the mainstay of treatment for many years, so new recommendations relegating digoxin should be evidence based and safe. We believe that little evidence exists that monotherapy with β blockers or calcium channel blockers improves exercise tolerance compared with digoxin. On the contrary, there is clear evidence that when β blockers are used alone, exercise capacity may worsen, especially in people with a history of heart failure.

Similarly, little evidence exists that monotherapy with these drugs improves heart rate control at rest and during exercise compared with digoxin alone. Beneficial effects on heart rate variability, together with improved exercise tolerance, have only been shown with the combination of digoxin and a β blocker or calcium channel blocker. We believe that the combination of digoxin and a β blocker or calcium antagonist should be recommended as first line management. We emphasise that it is safest to start treatment with digoxin first.

All references are in the version on bmj.com

Meningitis after cochlear implantation

The risk is low, and preventive measures can reduce this further

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Since the 1980s, more than 80 000 people have received cochlear implants worldwide.[1] These implants are designed to enable people who are severely or profoundly deaf to experience sound and speech. Since 1990, implantation has become standard treatment for people who cannot communicate effectively despite well fitted hearing aids.[2] Children who are deaf when they are born can perceive sound and learn to speak if they receive cochlear implants at a young age (ideally under 18 months).[3] The use of cochlear implants has been thought to be safe.[4] But since 2002 the number of patients with meningitis related to cochlear implantation has increased worldwide.[5] Mortality and neurological complications after meningitis are high. We need to investigate the reasons for this and look at measures to reduce them.

Streptococcus pneumoniae is the most common organism involved.[6 7] The incidence of pneumococcal meningitis was found to be more than that of an age matched cohort in the general population.[6 8] Risk factors include: a particular design of implant (withdrawn from the market in 2002); inner ear malformations; leakage of cerebral spinal fluid after implantation; presence of a ventriculoperitoneal shunt; and a history of otitis media.[6 8]

An animal model of implant related pneumococcal meningitis has been developed.[9] This model has been used to quantify the bacterial threshold for pneumococcal meningitis and to study the pathogenesis of the disease and interventional strategies for reducing risk.[10] A laboratory study showed that the presence of a cochlear implant in healthy animals reduced the number of bacteria needed to induce pneumococcal meningitis and therefore increased the risk of meningitis.[11] Moreover, the surgical insertion of the implant, which involves fracturing the bony structures of the inner ear, was also an independent factor for subsequent risk of pneumococcal meningitis.[12]

Patients and their carers need to be informed of the risk of developing meningitis after implantation. This is especially true for patients with pre-existing risk factors. Patients should be told that although a cochlear implant increases the relative risk of pneumococcal meningitis compared with the age matched population, the absolute risk of meningitis is still low and the benefits of the implant outweigh this low risk.[6 7 13]

What can be done to reduce the risk of meningitis? The risk of developing meningitis after cochlear implantation can be lowered by implementing several strategies.[7] All implant recipients should be given vaccines that cover *Streptococcus pneumoniae* as recommended by the US Centers for Disease Control and Prevention.[14] Patients who develop symptoms of acute otitis media or bacteraemia should be assessed and treated urgently.[7] This is particularly important for recipients of cochlear implants who have other pre-existing risk factors. Oral antibiotics may be adequate for most episodes of uncomplicated acute otitis media in implant recipients. Intravenous antibiotics should be combined with mastoid drainage to prevent meningitis in recipients with mastoiditis.[7] We recommend the insertion of tympanostomy tubes and the use of prophylactic antibiotics in implanted children prone to otitis media until they grow out of their susceptibility to otitis media.

All references are in the version on bmj.com