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Developing role of HPV in cervical cancer prevention

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Since the Cervical Screening Programme was introduced in England, the incidence of cervical cancer has fallen by 44% and number of deaths from the disease by 70% (fig 1). This effect has also been seen in other countries.[1 2] The discovery of human papillomavirus (HPV) DNA in cervical cancer and in subsequent molecular biology and epidemiological studies shows that persistent cervical infection with "high risk" HPV types is a necessary cause of cervical cancer. This finding has led to two major developments in cervical cancer control: immunisation as a means of primary prevention and HPV testing in cervical screening, which is poised to replace cytology as the primary screening modality. This article reviews the evidence base for evolving from exfoliative cytology alone to a dual approach of HPV vaccination and HPV based cervical screening.

SOURCES AND SELECTION CRITERIA

We included evidence based on randomised trials of screening and vaccination, where these have been performed, and other high quality studies including prospective cohort studies, case control studies, and systematic reviews. Studies were limited to those published within the past five years, wherever possible. Widely cited references dealing with individual points that were published before this review were also used as appropriate.

SUMMARY POINTS

- Prophylactic vaccination against human papillomavirus (HPV) types 16 and 18 is predicted to further reduce deaths from cervical cancer, among a screened population
- Vaccinated women should participate in cervical screening
- Vaccination will also reduce referrals to colposcopy and the number of women who require treatment for high grade, cervical intraepithelial neoplasia
- Vaccination against HPV types 6 and 11 will result in a decline in genital warts
- HPV testing in the screening programme is now routinely used in England to triage women with low grade cytological abnormalities for colposcopy referral, and similarly for test of cure after treatment
- HPV negative women are at very low risk and can avoid the need for repeated annual recall, and screening intervals could be extended
- Secondary prevention based on HPV testing with a simple treatment algorithm, if feasible in developing countries, might prevent many deaths
- If primary prevention through vaccination were implemented in developing countries, millions of deaths from cervical cancer could be prevented over the next 50 years

Who is at risk of cervical cancer?

Risk factors for cervical cancer include early age at first coitus, non-barrier contraception, multiple partners, and low socioeconomic status, which are all associated with an increased risk of acquiring genital HPV infection. Other risk factors—notably smoking[4] and combined oral contraceptive use[5]—probably reflect a reduced capacity to clear an established HPV infection. Cervical HPV infection is common in young, sexually active women. A prospective English randomised study found that 40% of 20-24 year old women were HPV positive.[6] HPV infection becomes steadily less prevalent with age as a result of clearance and reduced opportunity for reinfection (fig 2).[6]

Most infections are harmless and short lived, but some persist and could cause cervical intraepithelial neoplasia (CIN) and invasive cervical cancer. Cervical cancer is a relatively uncommon consequence of persistent, high risk HPV infection, and takes 10 or more years to develop. Thirteen high risk types (including 16, 18, 31, 33, 35, 45, 52 and 58) are known to cause cervical cancer, but HPV 16 and 18 are the most important, contributing to more than 70% of cancers worldwide.[7] A proportion of CIN, mainly low grade, will regress spontaneously over a 12 to 24 month period. The increased risk of cancer, particularly from high grade CIN, is the basis for screening and treatment of precancerous lesions, although it is not currently possible to determine which lesions will regress or which will progress to cancer. In countries with organised cervical screening programmes, failure to attend for regular screening by cervical cytology is the most important risk factor for cervical cancer currently,[8] although this will evolve in coming years to include failure to receive HPV immunisation.

How effective is cervical screening?

The effectiveness of cervical screening undoubtedly varies, and is influenced by the following factors: the presence of an organised programme, high population coverage, repeated screening, the screening interval, training and quality assurance of staff in all disciplines, and effectiveness of treatment of detected abnormalities. The sensitivity

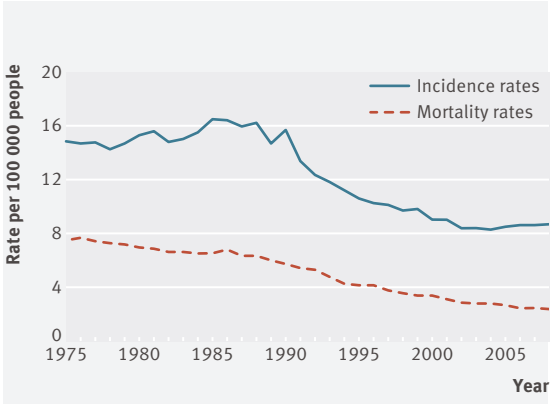

Fig 1 | Age standardised rates of cervical cancer incidence and mortality per 100 000 women in Great Britain[3]

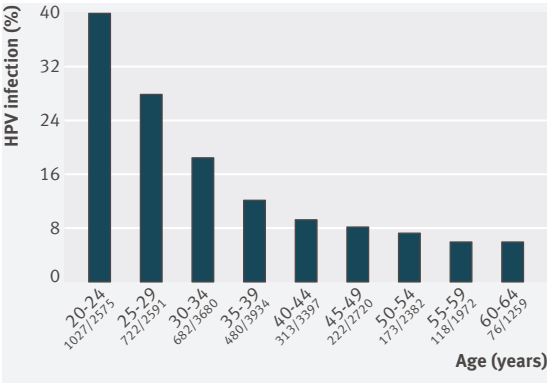

Fig 2 | Prevalence of high risk HPV according to five year age groups.[6] The numbers below each bar represent the number of people testing positive over the total number of people tested within each age group

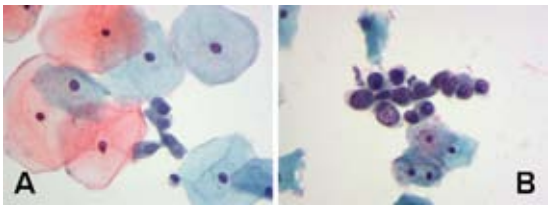

Fig 3 | ThinPrep liquid based cytology sample. Papanicalaou stain, magnification×400. (A) Normal cervical cytology. (B) Severe dyskaryosis equivalent to high grade squamous intraepithelial lesions in the Bethesda classification system; severely dyskaryotic cells are characterised by granular, irregularly distributed chromatin; the cells shown also have a high nuclear:cytoplasmic ratio and hyperchromatic nuclei

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of a single cervical smear is difficult to calculate, but the HART study,[9] which used conventional cytology, showed a sensitivity of 76% in the detection of high grade CIN. The overall sensitivity of cervical screening is, however, highly dependent on repeated screens at regular intervals.

Although liquid based cytology has not been found to be more sensitive or more specific than conventional cytology,[10] its introduction across the United Kingdom, aimed at reducing the rate of inadequate smears, means that reflex cytology and HPV tests can now be performed from the same sample. Peto and colleagues have estimated that cervical screening with cytology in England has prevented 80% of deaths from cervical cancer.[11] Cervical cytology has been the mainstay of cervical screening for decades, and although no organised national screening programme has yet fully implemented any other system, it is possible that primary HPV testing will in time replace cytology.

What improvements can HPV testing offer?

Cervical cytology is labour intensive and requires grading from borderline through mild dyskaryosis (low grade) to moderate and severe dyskaryosis (high grade). These categories are roughly equivalent to atypical cells of undetermined significance, low grade squamous intraepithelial lesions, and high grade squamous intraepithelial lesions in the US Bethesda classification, which is widely used outside of the UK. Although there is little difficulty distinguishing between normal cytology and high grade abnormality (fig 3), the classifications of normal and borderline changes have greater variation.

By contrast, HPV testing results in a positive or negative result and is less labour intensive, especially when using high throughput automated platforms. Primary cervical cytology leads to the identification of a large number of women with low grade abnormalities, and HPV testing can be used as a reflex test to identify the HPV negative abnormalities, which are benign. The clinical value of HPV testing therefore lies both in the sensitivity of a positive test and the high negative predictive value of a negative test, which distinguishes women who might need further investigation from those who can be returned to routine recall.

Strategies for exploiting HPV testing in cervical screening programmes

Secondary HPV testing (triage) of low grade abnormalities identified by primary cytology, before referral to colposcopy

This approach was shown to be more effective than repeat cytology in a large randomised trial from the United States,[12] and after initial piloting had been implemented prior to roll-out of triage of borderline and mild cytology, which began across England in April 2012. The pilot evaluation showed that 53% of women with borderline cytology and 83% of women with mild dyskaryosis tested positive for high risk HPV, of whom 16.3% were found to have high grade CIN.[13] The large proportion of women who are high risk HPV negative can therefore be safely returned to routine recall even in the presence of low grade cytological abnormalities, as well as HPV positive women whose colposcopy was satisfactory and negative.[14] This strategy avoids the need for multiple repeat cytology and the difficulty created by defaulting.

HPV as test of cure after treatment of CIN

Women have traditionally been screened at increased frequency for prolonged periods after treatment of CIN because of the risk of treatment failure. Several studies, including a large prospective study from the UK,[15] have shown that a negative result from a high risk HPV test after treatment, even if low grade cytological abnormalities are still present, indicates a very low risk of recurrent disease, such that routine recall intervals are again appropriate. This approach has the huge advantage of reducing the period when a woman is labelled as "not normal" and "at risk," from more than 10 years to less than one year. In a subsequent and larger "real life" pilot study, around 85% of treated women were HPV negative at six months after treatment.[13]

Use of HPV test as the primary screening test

Owing to concerns about the variable sensitivity of cytology, the consistently higher sensitivity of high risk HPV testing has led to consideration of HPV testing as the primary screening test. The problem is that infection with HPV is common, especially among younger women,[16] and therefore the specificity of HPV testing alone is too low to be clinically useful. Indeed, some international guidelines state that HPV testing should not be used in primary screening below age 30.[17 18] The prevalence of HPV infection is high among women in their late teens and early 20s and falls steadily until age 50 years (fig 2). The negative predictive value of a negative HPV test is, however, extremely high at all ages, indicating not only a very low risk of having high grade CIN, but also a low risk of developing it in the

future. The duration of this protection probably extends to six years[19 20] or beyond,[21] and it is in this area in particular that HPV testing outperforms cytology.

Current models of HPV testing as a screening modality need secondary testing of high risk HPV positives by cytology, which combines the higher specificity of cytology for high grade abnormality with the higher sensitivity of HPV testing (fig 3). Randomised controlled trials over two screening rounds in several European settings have validated this approach.[15 22-24] In a large randomised study within the Finnish screening programme, follow-up after a single round of screening showed that HPV screening with cytology triage detected more cases of CIN grade III than conventional cytology.[25] A pilot of implementation of HPV primary screening has recently started in England, which will identify practical issues of conversion.

The most difficult aspect of this strategy is managing women who are HPV positive and cytology negative. These women are at twice the risk of being infected with HPV compared with the population as a whole,[19] and therefore need early recall. If the HPV infection persists over a year, they probably warrant referral to colposcopy. Some studies have indicated that genotyping and onward referral of women who are positive for HPV type 16 or 18 could have value,[26] and some of the new HPV testing kits can provide a type 16 or 18 readout in addition to the generic positive result for high risk HPV. Although studies have shown some negative attitudes toward receiving a positive result,[27] there does not seem to be any sense of public rejection of HPV testing on this basis.

Should women younger than 25 years be screened?

Effective cervical screening requires a screening test that achieves a beneficial balance between sensitivity and specificity in the detection of high grade CIN, treatment of which prevents cancer. In the main, exfoliative cytology achieves this objective with a reduction in the incidence of cervical cancer. However, in women aged 20-24 years, the prevalence of low and high grade CIN is high in comparison with other age ranges, but the incidence of cancer is very low, at around 1:30 000 per year. Furthermore, by the early 2000s, uptake of cervical screening in England by this age group was less than 50%.

A case-control study in 2003[28] clearly indicated that screening provided less protection from cervical cancer in women under age 40 years than in those aged 40 years and older, and that this reduced sensitivity required screening in the younger age range to be repeated at least every three years. It also showed that among the small number of cancers in women aged under 25 years, the majority had occurred despite previous screening. The same authors published a similar study in 2009,[8] which confirmed that screening women younger than 25 was not protective. On the basis of these data, cervical screening in the English national programme has excluded women under 25 years since 2004, since which time there has not been an increase in cancer in that age group. What has been apparent is that when these cancers do occur, too often pelvic examination has not been performed in primary care, resulting in unacceptable delay in referral. New clinical guidelines were published in 2010 recommending a speculum examination in young women who present with persistent abnormal vaginal bleeding.[29]

What are the HPV vaccines and why are they important?

Prophylactic vaccines generate HPV specific antibodies that bind to the virus and prevent it from infecting cervical epithelial cells. Although effective against incident HPV infection in naive individuals, such antibody responses cannot clear established disease. There are two prophylactic HPV vaccines licensed for prevention of cervical cancer, Cervarix and Gardasil.[30-32] These vaccines are made with type-specific recombinant proteins from the viral coat formed into virus-like particles (VLPs) that mimic the structure of the virus but do not contain viral DNA (and cannot cause the diseases they protect against). Both vaccines contain VLPs for HPV types 16 and 18. Gardasil also contains VLPs for HPV types 6 and 11, which cause genital warts.

Large international randomised clinical trials have shown that both vaccines, given intramuscularly in three doses within 12 months, are over 99% effective at preventing precancerous lesions associated with HPV types 16 or 18 in young women with no evidence of previous infection.[33 34] These vaccines offer some cross-protection against closely related high risk types. Efficacy is lower for women with existing infection and against an all lesions (irrespective of HPV type) endpoint. As yet no immune correlate of effective protection has been defined. Data are now emerging that indicate that two doses of vaccine could be as protective as three.[35 36]

Mathematical modelling studies have combined estimates of vaccine efficacy, HPV prevalence, and sexual behaviour together with natural history parameters and cervical screening data, to show the variations in effectiveness and cost effectiveness that could be expected from immunisation programmes targeting different ages and different populations.[37-39] Many countries have introduced immunisation programmes targeting girls in late childhood and early adolescence, before the onset of sexual activity. In the UK, with careful attention to public health information and the logistics involved, uptake in the schools based programme has been around 85%. Several countries have already observed the expected falls in rates of vaccine-type infection among immunised individuals and populations.[40 41]

Modelling studies have also shown that the inclusion of young boys in immunisation programmes could probably increase the speed and magnitude of reduction in cervical cancer, but at a far higher ratio of cost to benefit.[42] The cost effectiveness of including boys is particularly sensitive to coverage in girls and to the benefits of prevention of cancers that occur in boys (such as oropharyngeal and anal), as well as genital warts. In 2011 and 2012, the US and Australia, respectively included boys in publicly funded immunisation programmes (using the quadrivalent vaccine).

The direct protective effects of immunisation and of screening are similar, with each having the potential of 70-80% efficacy against cervical cancer in the long run. However, the primary prevention offered by immunisation

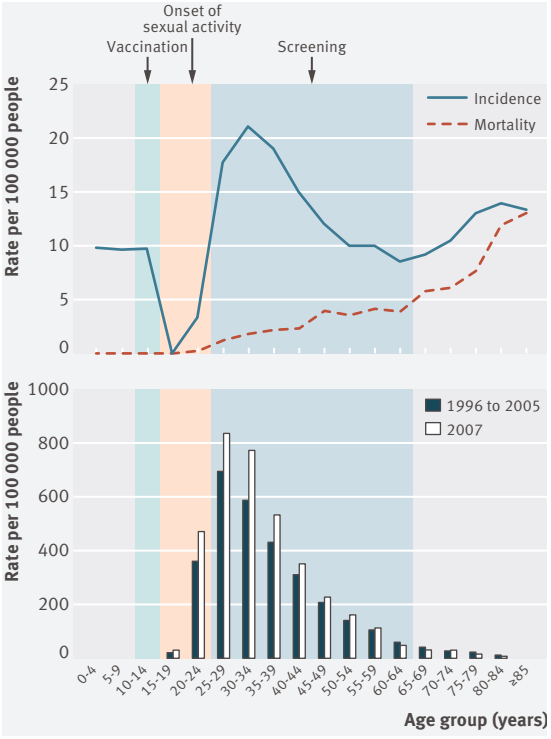

Fig 4 | Age related rates of incidence and mortality for cervical cancer and treatment for CIN shown against the age ranges for vaccination, onset of sexual activity, and cervical screening. Upper graph shows incidence and mortality rates for cervical cancer in the UK by age, in 2008.[3] Lower graph is derived from data showing the proportion of women undergoing treatment for CIN by age (Denmark).[45] The background provides the age ranges for prophylactic vaccination, onset of sexual activity, and cervical screening

brings important improvements to the secondary prevention offered by cervical screening, even with the obvious benefits of the longer duration of protection. A growing number of observation studies are confirming that immunisation programmes in UK schools with uptake of about 85%[43] are capable of achieving more equitable protection across social class than cervical screening. Epidemiological studies are starting to show evidence of herd immunity, resulting from the prevention of infection transmission by vaccinated individuals, conferring benefit on individuals who are unvaccinated. Australian data show that the incidence of genital warts is falling in heterosexual men as a consequence of high coverage of female vaccination.[44] Furthermore, vaccination is likely to provide additional protection to women under the age of 30, in whom cytology is less effective.[17 18]

MESSAGES FOR WOMEN

HPV testing distinguishes women at very low risk from those at some risk

An HPV positive screening test must be accompanied by a cytology result to determine management

HPV immunisation will protect young women against infection by HPV 16 and 18 (and against genital warts if the quadrivalent vaccine is used)

HPV prophylactic vaccination does not treat established HPV infection and is less beneficial for women aged 25 years and older, in whom persistent HPV infection might be already established or whose remaining lifetime risk of new infection might be low

ADDITIONAL EDUCATIONAL RESOURCES

NHS Cervical Screening Programme (www.cancerscreening.nhs.uk/cervical/)—a repository of documents that describe the quality of care standards and algorithms followed in the English cervical screening programme

Jo's Cervical Cancer Trust (www.jostrust.org.uk/)—provides women with useful information and advises about cervical screening

ASCCP clinical practice guideline (www.asccp.org/ConsensusGuidelines/UpdatedConsensusGuidelines/tabid/14181/Default.aspx)—Clinical practice guideline for the management of abnormal cervical cytology from the American Society for Colposcopy and Cervical Pathology in the United States

British Society for Colposcopy and Cervical Pathology (www.bsccp.org.uk/)—Educational resources for women and healthcare professionals in the UK regarding colposcopy

QUESTIONS FOR FUTURE RESEARCH

To what extent will the switch from cytology to HPV testing as the primary cervical screening modality result in a reduction in deaths from cervical cancer?

Will women who test HPV positive and cytology negative in such a programme comply with early recall?

How will women and providers, who are used to and trust cervical cytology, view HPV based screening?

Will the cytology triage in HPV positive women result in an increase in reporting of low grade abnormalities?

Are there other biomarkers that would provide more effective triage of HPV positive results than cytology?

Will a two dose vaccination schedule be considered?

Will vaccination mean that screening becomes unnecessary?

HPV immunisation before the onset of sexual activity, combined with cervical screening during the years when cervical abnormalities become common, can be viewed as a continuum in terms of prevention of cervical cancer (fig 4). Prophylactic vaccines given to uninfected individuals will reduce HPV associated cervical disease in the future, but this effect is reduced in women who have previously been exposed to HPV.[33 34] For women above the age eligible for vaccination, or vaccinated after exposure to HPV type 16 or 18, cervical cancer prevention will continue to rely solely on screening. Even in those adolescents who have been vaccinated against types 16 or 18, cervical cancer may be caused by other high risk types (currently in around 30% of cases). Polyvalent vaccines protecting against more of the HPV types associated with cervical cancer could become available in coming years. Until then, cervical screening will continue to offer an important reduction to the risk of cervical cancer in vaccinated populations, unless postvaccination surveillance studies show a far greater than expected reduction in high grade CIN.

Cost effectiveness studies have recommended in favour of HPV immunisation as an addition to, and not a substitute for, cervical screening. The benefits of population screening after the introduction of a vaccination programme will depend partly on as yet unknown factors, such as duration of protection, the uptake of immunisation, and the uptake of screening. Fears have been expressed that vaccinated women will consider themselves protected, and will not attend for screening. Postvaccination surveillance of young women entering screening will be important in assessing the effect of vaccination on screening uptake and disease prevention.

In an era of HPV based screening, a therapeutic vaccine that could clear HPV infection in the presence of abnormal—or indeed, normal—cytology could be very beneficial by reducing physical and psychological harm.[46] The development of therapeutic vaccines has been underway for some time, but none has reached the clinic yet. Challenges

include which HPV antigens to target, how best to deliver the antigens to the immune system, the most appropriate choice of adjuvant, and how to measure immunological responses and clinical efficacy.

How can HPV based strategies benefit women in the developing world?

The poorest countries of the world not only have the greatest burden of cervical cancer, but also they have healthcare systems that are least well equipped to treat the disease and that have little screening capacity. The benefits of cytological screening have largely not been realised in developing countries. A seminal randomised clinical trial in India among a previously unscreened population has shown HPV based screening to be capable of reducing the mortality from cervical cancer within 5 years.[47] The development of rapid HPV testing[48] can allow a simple algorithm, offering women who are high risk HPV positive rapid access to colposcopy or visual assessment following acetic acid (VIA) and treatment for an abnormality.[47]

HPV based screening also seems to be more feasible in low resource settings, avoiding the logistical complexity and expertise required by cytology. The costs of prophylactic vaccination could possibly be partially mitigated by using a two dose vaccination schedule—especially now that the GAVI Alliance has facilitated access for the poorest countries to a sustainable supply of HPV vaccines for as low as $4.5 (£2.9; €3.4) per dose. Vaccination has the potential to prevent deaths worldwide over the next 50 years, but requires the political will and determination to tackle what is now among the most common killers of women in impoverished countries.

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Corrections and clarifications

Klinefelter's syndrome—a diagnosis mislaid for 46 years

We have been informed that there is an error in the Clinicians' perspectives section of this Patient's Journey (*BMJ* 2012;345:e6938, print publication 5 Jan 2013, pp 34-35). The first paragraph of this section should have referred to hypergonadotrophic hypogonadism (not "hypogonadotrophic hypogonadism") as a feature of Klinefelter's syndrome.

Bed bug infestation

The authors of this Clinical review have alerted us to an error in the paragraph "What are bed bugs?" (*BMJ* 2013;346:f138, print publication 26 Jan, pp 30-33). The first line mixed up the preferred habitat of the *Cimex lectularius* and *Cimex hemipterus* species and should have read: "The two main species of bed bugs are *Cimex lectularius* and *Cimex hemipterus*, which are found in temperate areas and tropical zones, respectively."

Minerva

Kim To and colleagues, the authors of this Minerva photo item (*BMJ* 2013;346:f685, print publication 9 Feb, p 40), wish to make the following statement: "After publication of our article, we received an email from the admitting dermatology team at the Queen Elizabeth Hospital Birmingham saying that discussions with the patient's family revealed that the patient had had an absence seizure while boiling a kettle the day before his admission and had suffered a burn as a direct consequence. They therefore felt that the clinical presentation was more in keeping with scalds than with toxic epidermal necrolysis. At the time of presentation this aspect of the patient's history was not picked up despite repeated history taking from various clinicians. The patient had stated that the lesions were not there when he went to bed the night before and they were noticed by him first thing in the morning. The patient was transferred to Queen Elizabeth Hospital with a provisional diagnosis of toxic epidermal necrolysis after consultation with the local consultant dermatologist. Unfortunately, no further communication was received on this patient from the admitting trust after the patient's discharge, and several attempts at obtaining a copy of the discharge report from his general practitioner proved unsuccessful. This is why the final amended diagnosis has only now come to our attention."

Investigating urinary tract infections in children

An error occurred in this Rational Imaging article by A Davis and colleagues (*BMJ* 2013;346:e8654, print publication 9 Feb, pp 35-37). In figure 1 the right hand label is wrong: the two arrows point to the "dilated lower pole [not upper pole as published] collecting system"; the legend below the figure is correct.

Chronic exertional compartment syndrome

In this Easily Missed article by Ronald S Paik and colleagues (*BMJ* 2013;346:f33, print publication 23 Feb, pp 35-37) the figure showed "the cross sectional anatomy of the leg midway between the knee and ankle, including muscles and neurovascular structures in each of the four leg compartments." Unfortunately, the diagram failed to show the fascial layers. A revised figure outlining and naming the four different compartments is available on bmj.com.

Andrew Witty: the acceptable face of big pharma?

In this Feature article by Rebecca Coombes we mixed up our currency symbols (*BMJ* 2013;346:f1458, print publication 9 Mar, pp 16-18). GlaxoSmithKline's fine was correctly quoted as $3bn at the start of the article but later rose wrongly to £3bn. Also, we mistakenly spelt out the FDA as "the Food and Drink Administration," instead of the Food and Drug Administration.

Publishing cardiac surgery mortality rates: lessons for other specialties

Two errors occurred in figure 2 of the print version of this Analysis article by Ben Bridgewater and colleagues (*BMJ* 2013;346:f1139, print publication 9 Mar, pp 19-21). Firstly, the red "one sided 95% (dashed) confidence limit" mentioned in the caption was missing; secondly, the bottom value of the y axis should be 0, not 5. The online version is correct.

The hospital bed: on its way out?

We made a mistake in the numbering of the y axis of figure 3 in this Data Briefing article by John Appleby (*BMJ* 2013;346:f1563, print publication 16 Mar, pp 16-17). The top three numbers (upwards) should be 85, 90, 95 [not 95, 80, 95 as published].

Diagnosis and management of carotid atherosclerosis

We have been alerted to an error in this Clinical Review by Ankur Thapar and colleagues (*BMJ* 2013;346:f1485, print publication 23 Mar, pp 29-33). In the legend under figure 2, STA should have been spelt out as "superior thyroid artery" [not "superficial temporal artery" as published].

Implementation of the Health and Social Care Act

The author of this Editorial, Nigel Edwards, would like to clarify that the second paragraph should have referred to 23 commissioning support units, not "23 clinical support units," as published (*BMJ* 2013;346:f2090, print publication 6 Apr, p 5).