Safety of tiotropium

Indirect evidence suggests the Respimat inhaler is riskier than the Handihaler

RESEARCH, p 1348

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Competing interests: The author has completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work
Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2011;342:d2970
doi: 10.1136/bmj.d2970

Tiotropium is used to treat chronic obstructive pulmonary disease via two different inhaler devices: the original Handihaler (18 µg once daily), which uses a powder formulation, and the newer Respimat mist inhaler (5 µg once daily). The two devices cannot be assumed to have the same safety profile, however, and the linked systematic review by Singh and colleagues assessed all cause mortality in people with chronic obstructive pulmonary disease using the Respimat mist inhaler.[1]

DR P MARAZZI/SPL

An ongoing trial will provide more certainty about the comparative safety of tiotropium inhaler devices

The authors assessed the risk of all doses of tiotropium given via the mist inhaler (including 10 µg daily), but because the usual dose in clinical practice is 5 µg daily, this editorial will focus on the safety results for this dose only. The review reported a 46% relative increase in risk of mortality from any cause in patients using the mist inhaler compared with placebo (relative risk 1.46, 95% confidence interval 1.01 to 2.10). Relative risks and odds ratios are used in meta-analyses because they tend to be more stable across trials of different durations and with participants at different baseline risks. However, it is misleading to describe the effect as a 46% increased risk of dying.

The impact of the relative risk depends on the baseline risk of the patient concerned. In this case, in trials that lasted for a year, 47 of 2655 participants taking placebo died, which gives a mortality risk of 1.8% a year. In the same trials, 68 of the 2659 participants taking 5 µg of tiotropium via the mist inhaler died, which gives a mortality risk of 2.6% a year. The 46% relative increase in risk therefore represents an absolute difference of 0.8%, because death was a rare event. The difference in absolute risk is shown in the Cates plot (www.nntonline.net/visualrx/cates_plot/; figure), in which 18 deaths occurred in the trials for each 1000 patients treated for a year with placebo, and an extra eight occurred in those treated with tiotropium via the mist inhaler. This translates into an annual number needed to treat for one additional participant to suffer harm (NNT(H)) of 121 patients given 5 µg tiotropium for a year for one additional death compared with patients given placebo. There is considerable uncertainty around this estimate, and the 95% confidence interval runs from anywhere between NNT(H) of 51 and 5556. However, this point estimate of the increased risk of mortality with the mist inhaler is considerably larger than that found for salmeterol in asthma (7/10 000 over 28 weeks).[2]

So how do we go about sharing this risk information with patients? What we really want to know is how the risk of the Respimat compares with that of the Handihaler. Although the UPLIFT trial did not report an increase in mortality in patients using the Handihaler, that trial differed greatly from those that looked at the Respimat, so differences between the delivery devices cannot be untangled from other differences between the trials.[3] More certainty about the comparative safety of the two devices will have to wait for the results of the ongoing randomised trial mentioned by Singh and colleagues,[4] which directly compares tiotropium delivered by the Handihaler (18 µg a day) or the Respimat (5 µg and 2.5 µg a day).

The improved delivery afforded by the mist inhaler could possibly increase plasma concentrations of tiotropium and therefore increase risks. Could the excess mortality in the Respimat trials be caused by the inclusion of patients who are taking 10 µg a day? This is unlikely, because risk in patients taking the 5 µg dose was still significantly increased. The Medicines and Healthcare Products Regulatory Agency currently advises caution when using the mist inhaler in patients with arrhythmias and that the recommended daily dose should not be exceeded.[5]

So where do we go from here? Pending the results of the head to head trial, the indirect evidence that is currently available suggests that the Handihaler is a safer bet than the Respimat. If patients have a strong preference for the mist inhaler, the possible increased risk in mortality will need to be shared with them, and the Cates plot might help to make this easier.

Response on bmj.com

"Obtaining a clinically significant difference in these trials is like winning an Olympic medal with statistical significance the equivalent of finishing fourth or fifth."
R Andrew McIvor, professor of medicine, McMaster University, Hamilton, Ontario, Canada
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1 Singh S, Loke YK, Enright PL, Furberg CD. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2011;342:d3215.
2 Cates CJ, Cates MJ. Regular treatment with salmeterol for chronic asthma: serious adverse events. *Cochrane Database Syst Rev* 2008;3:CD006363.
3 Celli B, Decramer M, Kesten S, Liu D, Mehra S, Tashkin DP; UPLIFT Study Investigators. Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009;180:948-55
4 Comparison of tiotropium in the HandiHaler versus the Respimat in chronic obstructive pulmonary disease. NCT01126437. *ClinicalTrials.gov*http://clinicaltrials.gov/ct2/show/NCT01126437.
5 Medicines and Healthcare Products Regulatory Agency. Tiotropium: safety studies of Spiriva Respimat. 2010. www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON099869.

Treatments for common and plantar warts

Salicylic acid or liquid nitrogen is probably no more effective than a wait and see policy

RESEARCH, p 1349

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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work
Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2011;342:d3119
doi: 10.1136/bmj.d3119

Cutaneous warts are common, benign, and usually self limiting papillomas.[1 2] They present in various forms and sizes and are caused by infection with human papillomavirus (HPV).[1 2] The two most common types are common warts (verrucae vulgaris), which usually occur on the hands, and plantar warts (verrucae plantares), which are usually found on the soles of the feet. Between 10% and 30% of primary school children have cutaneous warts, of which two thirds resolve within two years.[3] In the linked randomised controlled trial, Cockayne and colleagues compare the effectiveness of cryotherapy versus salicylic acid for the treatment of plantar warts.[4]

Treatments have been based on destruction (cryotherapy, photodynamic treatment, pulsed dye laser), keratolysis (salicylic acid), immunostimulation (dinitrochlorobenzene, interferons), or antimitotic effects (bleomycin, fluorouracil).[1 5] A systematic review of topical treatments for cutaneous warts was published in 2006 and updated in 2009 to include subsequent randomised controlled trials.[5 6] The authors identified 78 relevant studies, most of which were of low methodological quality, and concluded that the only evidence based treatments were salicylic acid and aggressive cryotherapy.[5] In practice, many warts will need a combination of treatments.[7] Also, because most modalities are user dependent, individual practitioners may have higher or lower success rates than that reported in the literature.[7]

A subsequent randomised controlled trial of 250 participants in primary care compared cryotherapy with liquid nitrogen every two weeks, self application of salicylic acid daily, or a wait and see approach. It found that cryotherapy was the most effective treatment for common warts but found no clinically relevant difference between the three approaches for plantar warts after 13 weeks.[8]

Cockayne and colleagues' study investigated 240 patients aged 12 years or more with plantar warts.[4] In one group of patients, a healthcare professional delivered cryotherapy using liquid nitrogen two to three weeks apart for a maximum of four treatments. This treatment was compared with daily self treatment with 50% salicylic acid for a maximum of eight weeks. The trial found no significant difference in the proportions of participants with complete clearance of all plantar warts at 12 weeks between the salicylic acid and cryotherapy groups (14.3% *v* 13.6% clearance).[4] Although no group was allocated to a wait and see approach, the cure rates after intervention are probably not higher than without intervention, as was found in the previous trial.[8]

CHASSENET/SPL

Treatments that target the specific type of HPV in the wart could be the way forward

The patients in Cockayne and colleagues' study were 12 years or more, whereas the incidence of warts is highest in those aged 5-14.[9] The low clearance rates they found are probably not applicable to patients under 12 years because plantar warts in children are less persistent than in adolescents and adults.[8] Spontaneous clearance rates are much higher in younger children than in those aged 12 years or more, and cryotherapy and salicylic acid are not more effective than a wait and see approach.[8] Although it may be best not to treat cutaneous warts, some cases may warrant treatment, such as those associated with considerable social stigma, especially when lesions are on the face and hands.[5] Warts that cause pain, such as those on the soles of the feet or close to nails, may also warrant treatment.[5]

Because currently available treatments for plantar warts often fail, future research should not only focus on new treatments, but also try to identify subgroups of patients who will respond to specific treatments. Large numbers of HPV types, distributed over five genera, infect the human skin.[10] HPV types belonging to four of those genera—alphapapillomaviruses, gammapapillomaviruses, mupapillomaviruses, and nupapillomaviruses—have been detected in cutaneous warts. Little is known about the epidemiology and prevalence of these HPV types that cause common and plantar warts. Reliable detection and sampling techniques are needed to study the epidemiology of these HPV infections and have only recently become available.[11] This assay detects and identifies DNA of all known wart associated HPV types from the alphapapillomaviruses (HPV types 2, 3, 7, 10, 27, 28, 29, 40, 43, 57, 77, 91, 94), gammapapillomaviruses (HPV types 4, 65, 95, 48, 50, 60, 88), mupapillomaviruses (HPV types 1 and 63), and

nupapillomaviruses (HPV41), but epidemiological studies using this technique are not yet available.

Definitive treatment for plantar warts remains elusive. Treatment with salicylic acid or liquid nitrogen is probably not more effective than a wait and see policy. Large scale HPV typing may teach us more about the epidemiology of plantar warts and which HPV types are preferentially present. HPV specific treatments that are based on the HPV type in the lesions may be the way forward. However, future treatments must be safe, preferably painless, and not increase morbidity.[7] This is especially important, because around two thirds of warts clear without treatment within two years.

1 Leung L. Recalcitrant nongenital warts. *Aust Fam Physician* 2011;40:40-2.
2 Jablonska S, Majewski S, Obalek S, Orth G. Cutaneous warts. *Clin Dermatol* 1997;15:309-19.
3 Van Haalen FM, Bruggink SC, Gussekloo J, Assendelft WJ, Eekhof JA. Warts in primary schoolchildren: prevalence and relation with environmental factors. *Br J Dermatol* 2009;161:148-52.
4 Cockayne S, Hewitt C, Hicks K, Jayakody S, Kang'ombe AR, Stamuli E, et al. Cryotherapy versus salicylic acid for the treatment of plantar warts (verrucae): a randomised controlled trial. *BMJ* 2011;342:d3271.
5 Kwok CS, Holland R, Gibbs S. Efficacy of topical treatments for cutaneous warts: a meta-analysis and pooled analysis of randomized controlled trials. *Br J Dermatol* 2011; online 11 January.
6 Gibbs S, Harvey I. Topical treatments for cutaneous warts. *Cochrane Database Syst Rev* 2006;3:CD001781.
7 Boull C, Groth D. Update: treatment of cutaneous viral warts in children. *Pediatr Dermatol* 2011; online 26 April.
8 Bruggink SC, Gussekloo J, Berger MY, Zaaijer K, Assendelft WJ, de Waal MW, et al. Cryotherapy with liquid nitrogen versus topical salicylic acid application for cutaneous warts in primary care: randomized controlled trial. *CMAJ* 2010;182:1624-30.
9 Westert GP, Schellevis FG, de Bakker DH, Groenewegen PP, Bensing JM, van der Zee J. Monitoring health inequalities through general practice: the Second Dutch National Survey of General Practice. *Eur J Public Health* 2005;15:59-65.
10 Bernard HU, Burk RD, Chen Z, Van DK, Hausen H, de Villiers EM. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. *Virology* 2010;401:70-9.
11 De Koning MN, Ter Schegget J, Eekhof JA, Kamp M, Kleter B, Gussekloo J, et al. Evaluation of a novel broad-spectrum PCR-multiplex genotyping assay for identification of cutaneous wart-associated human papillomavirus types. *J Clin Microbiol* 2010;48:1706-11.

Should pregnant women sleep on their left?

The suggestion that this may help to prevent late stillbirth requires further study

RESEARCH, p 1350

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Cite this as: BMJ 2011;342:d3659
doi: 10.1136/bmj.d3659

The United Kingdom has one of the highest rates of stillbirth in the developed world.[1] More than 4000 infants were stillborn in the UK in 2009 (out of about three million worldwide), and 1200 of these stillbirths occurred at or after 37 weeks' gestational age.[2] In high income countries, there are 10 times more stillbirths than deaths from sudden infant death syndrome—the subject of a major campaign.[3] Stillbirth affects four times more babies than Down's syndrome. A sophisticated screening programme is recommended and widely offered for Down's syndrome, yet screening for stillbirth in the general population is confined to measurement of the external size of the uterus with a tape measure at each visit, according to the current National Institute for Health and Clinical Excellence Antenatal Care guideline.[4] Any simple intervention that reduces the risk of stillbirth would be extremely welcome. Could the linked study, in which Stacey and colleagues found an association between maternal sleep position and risk of stillbirth,[5] constitute the basis for a "not back to sleep" campaign for pregnant women?

Evidence based guidelines on sleep in pregnancy from professional organisations are sparse. Advice on the internet abounds, but much of it is derived by extrapolation from other contexts. The theory is that if a woman lies supine the gravid uterus may compress the inferior vena cava, resulting in reduced venous return and limited uteroplacental blood flow. A study of 22 women after 36 weeks' gestation showed that placental intervillous blood flow was about 25% lower in the supine compared with the left position.[6] But in healthy third trimester women with normal size babies, there is only limited evidence that supine positioning in antenatal women,[7] or in women undergoing caesarean section,[8] is associated with any significant change in fetal indices. However, in clinical situations involving pregnant women, it is standard practice to favour left lateral tilt over other positions, and it is plausible that this position may be better for the baby in other contexts.

Stacey and colleagues compared women who had had a late stillbirth with pregnant control women, who were matched for gestational age but went on to deliver a healthy baby. In addition to sleep position they analysed 15 other risk factors, and some of the findings have been reported elsewhere.[9] The key questions in interpreting this study are: is the observed significant association between maternal sleep position on the night before the stillbirth a chance finding? Can it be explained by bias? Could it be reverse causation?

The current study identifies eight classifications of sleep position, each containing four groups. Randomised controlled trials in which large numbers of comparisons are reported are not as reliable as those that report on a prespecified primary outcome because statistical significance will almost inevitably be seen when large numbers of outcomes are compared; trials now have to prespecify a primary outcome. The substantial number of comparisons in the linked study means that it must be considered as a hypothesis generating study rather than a hypothesis testing one.

As with any retrospective study, results may be explained by bias. Women who had experienced a stillbirth completed questionnaires 25 days after the event. A report of left sided sleeping position may be a surrogate measure of increased access to and uptake of sources of educational information, and it may act as a confounder for which adjustment for social deprivation level is insufficient. The authors did not present detailed information on cause of death in the stillbirth cases in this report, and the lack of any analysis of cause of death as an influential variable makes it difficult to assess the biological plausibility of the study's findings. A greater association between non-left sided sleep position and stillbirth in fetuses vulnerable to impaired uteroplacental blood flow, such as those with growth restriction, would add weight to the finding. Stillbirth is a descriptor of heterogeneous

events that lead to death; future research should elucidate which pregnancies are most likely to benefit.

There is a strong possibility that part of the association can be explained by reverse causation. Reduced fetal movement is one of the most common symptoms seen before stillbirth. Moreover, in many cases delay occurs between intrauterine fetal death and its confirmation by a health professional. In a proportion of cases of stillbirth in this study, the baby may have died before the last sleep night reported by the mother. Compromised babies may have reduced movements in the days leading up to the death. Hence, rather than being a cause of stillbirth, the associations between longer sleep and not rising during the night in the week before stillbirth may reflect absent or reduced fetal movements, as a consequence of the baby's death.

A forceful campaign urging pregnant women to sleep on their left side is not yet warranted. Further research is needed before the link between maternal sleep position and risk of stillbirth can be regarded as strongly supported. If these findings are validated in a future study, advice on sleep position is an intervention that would be relatively easy to implement. The message is appealing, perhaps partly because of resonance with the campaign on changing sleep position for infants, which led to a marked reduction in rates of sudden infant death.[10] However, the impact of a similar intervention in pregnancy is uncertain. A previous study in which pregnant women over 30 weeks' gestation admitted to the antenatal ward were directly observed reported that most (77%) women slept with a left tilt,[11] which is higher than the proportion of controls who reported left sided sleep in the current study. Although the message for mothers to sleep on their left is probably harmless and may be helpful, this study should be seen as one that only generates a hypothesis that needs validation.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Commissioned; not externally peer reviewed.

1 Cousens S, Blencowe H, Stanton C, Chou D, Ahmed S, Steinhardt L, et al. National, regional, and worldwide estimates of stillbirth rates in 2009 with trends since 1995: a systematic analysis. *Lancet* 2011;377:1319-30.
2 Centre for Maternal and Child Enquiries (CMACE). Perinatal mortality 2009. 2011. www.cmace.org.uk/Publications-Press-Releases/Report-Publications/Perinatal-Mortality.aspx.
3 Information and Statistics Division NHS Scotland. Scottish perinatal and infant mortality report 2000. 2001. www.isdscotlandarchive.scot.nhs.uk/isd/files//mat_spimmr_report01.pdf.
4 National Institute for Health and Clinical Excellence. Antenatal care: routine care for the healthy pregnant woman. CG62. 2008. www.nice.org.uk/nicemedia/pdf/CG062NICEguideline.pdf.
5 Stacey T, Thompson JMD, Mitchell EA, Ekeroma AJ, Zuccollo JM, McCowan LME. Association between maternal sleep position and risk of late stillbirth: a case-control study. *BMJ* 2011;342:d3403.
6 Kauppila A, Koskinen M, Puolakka J, Tuimala R, Kuikka J. Decreased intervillous and unchanged myometrial blood flow in supine recumbency. *Obstet Gynecol* 1980;55:203-5.
7 Ellington C, Katz VL, Watson WJ, Spielman FJ. The effect of lateral tilt on maternal and fetal hemodynamic variables. *Obstet Gynecol* 1991;77:201-3.
8 Cluver C, Novikova N, Hofmeyr GJ, Hall DR. Maternal position during caesarean section for preventing maternal and neonatal complications. *Cochrane Database Syst Rev* 2010;6:CD007623.
9 Stacey T, Thompson JM, Mitchell EA, Ekeroma AJ, Zuccollo JM, McCowan LM. Relationship between obesity, ethnicity and risk of late stillbirth: a case control study. *BMC Pregnancy Childbirth* 2011;11:3.
10 National Institutes of Health: Eunice Kennedy Shriver National Institute of Child Health and Human Development. Back to sleep public education campaign. www.nichd.nih.gov/SIDS/upload/SIDS_rate_back_sleep_2006.pdf.
11 Mills GH, Chaffe AG. Sleeping positions adopted by pregnant women of more than 30 weeks' gestation. *Anaesthesia* 1994;49:249-50.

H1N1 influenza in pregnant women

Vaccination is the key to mitigating the higher incidence of adverse outcomes

RESEARCH, p 1351

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Cite this as: *BMJ* 2011;342:d3237
doi: 10.1136/bmj.d3237

Although the 2009 H1N1 pandemic proved to be more benign than anticipated, it had a substantial effect on pregnant women. In the linked cohort study, Pierce and colleagues report the perinatal outcomes of 256 pregnant women admitted to hospital with H1N1 influenza in the United Kingdom.[1]

The study found that pregnant women admitted to hospital with H1N1 influenza had significantly higher rates of adverse pregnancy outcomes than uninfected pregnant women. These included three to four times higher rates of preterm birth, four to five times higher rates of stillbirth, and four to six times higher rates of neonatal death.[1] These high rates of adverse perinatal outcomes were consistent with those reported in a population based study from the United States,[2] which also found a high maternal death rate (five deaths in 489 pregnant women admitted to hospital). Presumably, details of specific maternal complications and causes of death will be forthcoming from both the UK and the US.

Pregnant women admitted to hospital with either seasonal flu or H1N1 influenza had substantially lower rates of pre-existing morbidity compared with non-pregnant women admitted to hospital for the same infection.[2] Clearly, pregnancy is an important risk factor for severe illness in women with seasonal flu or H1N1 influenza.[3] In addition, H1N1 influenza seems to be more virulent than the seasonal form of the disease. The US study found that a higher proportion of pregnant women with H1N1 infection were admitted to intensive care units compared with pregnant women with seasonal flu.[2]

Only 7% of the pregnant women admitted to hospital with H1N1 infection in the US study had received the H1N1 vaccine. This contrasts with surveys in the US showing that 47% of pregnant women received H1N1 vaccine between October 2009 and March 2010.[4] Although these two sets of figures come from different studies and regions, the substantial difference in rates suggests that the vaccine is efficacious in preventing severe illness in pregnant women. Pierce and colleagues reported similar figures; only 5% of the pregnant women

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admitted to hospital had been vaccinated,[1] whereas vaccination rates in the population of pregnant women have been estimated to be 65%.[5] Various studies have shown that influenza vaccines are safe and efficacious,[6] so the public needs to be made more aware of the value of such immunisation in pregnancy. Women of reproductive age with pre-existing morbidity are also an important risk group who need to be informed.

The proportion of young pregnant women admitted to hospital with H1N1 influenza was unexpectedly high. In the UK, 10% of pregnant women admitted to hospital with H1N1 influenza were under 20 years (compared with 5% of pregnant women admitted to hospital without H1N1 influenza), whereas in the US, the proportion aged 15-24 years was 47.4% (compared with 34.3% of all women who delivered in the US in 2009[7]). Similarly, there was an excess of young women among pregnant women admitted to hospital with seasonal influenza.[2] This implies a low rate of vaccination or a higher susceptibility to severe illness in young pregnant women.[3] Irrespective of the mechanism responsible for the difference, public health efforts to improve the uptake of influenza vaccination by young pregnant women should be increased.

In the US study, pregnant women infected with H1N1 had a shorter hospital stay and were less likely to be admitted to intensive care if they received antiviral agents within two days of admission. Reports from the UK also showed reduced admission to intensive care after antiviral treatment.[5] In the UK study, H1N1 infection in the third trimester was most likely to lead to preterm delivery, but this association was not found in the US study.

Obesity and iatrogenic early delivery are additional factors that need to be considered. The UK study and others suggest that obesity is a risk factor for severe illness as a result of H1N1 influenza.[3] The high rates of stillbirth, despite a 40% caesarean delivery rate,[1] warrant a reconsideration of the appropriate indications and timing for caesarean delivery.

Conclusions drawn from these studies need to be interpreted cautiously because selective admission to hospital of pregnant women with seasonal flu or H1N1 influenza may have distorted risk factors or patterns of disease. Current evidence, including that from the UK Obstetric Surveillance System and the Centers for Disease Control and Prevention, suggests that influenza vaccination confers protection against serious illness and death, especially in pregnant women.

Competing interests: Both authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Commissioned; not externally peer reviewed.

1 Pierce M, Kurinczuk JJ, Spark P, Brocklehurst P, Knight M; on behalf of UKOSS. Perinatal outcomes after maternal 2009/H1N1 infection: national cohort study. *BMJ* 2011;342:d3214.
2 Creanga AA, Kamimoto L, Newsome K, D'Mello T, Jamieson DJ, Zotti ME, et al. Seasonal and 2009 pandemic influenza A (H1N1) virus infection during pregnancy: a population-based study of hospitalized cases. *Am J Obstet Gynecol* 2011; online 18 April.
3 Bautista E, Chotpitayasunondh T, Gao Z, Harper SA, Shaw M, Uyeki TM, et al. Writing Committee of the WHO: Consultation on clinical aspects of pandemic (H1N1) 2009 influenza. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. *N Engl J Med* 2010;362:1708-19.
4 Centers for Disease Control and Prevention (CDC). Seasonal influenza and 2009 H1N1 influenza vaccination coverage among pregnant women—10 states, 2009-10 influenza season. *MMWR Morb Mortal Wkly Rep* 2010;59:1541-5.
5 Yates L, Pierce M, Stephens S, Mill AC, Spark P, Kurinczuk JJ, et al. Influenza A/H1N1v in pregnancy: an investigation of the characteristics and management of affected women and the relationship to pregnancy outcomes for mother and infant. *Health Technol Assess* 2010;14:109-82.
6 Tamma PD, Ault KA, del Rio C, Steinhoff MC, Halsey NA, Omer SB. Safety of influenza vaccination during pregnancy. *Am J Obstet Gynecol* 2009;201:547-52.
7 Hamilton BE, Martin JA, Ventura SJ. Births: preliminary data for 2009. National vital statistics report. 2010. www.cdc.gov/nchs/data/nvsr/nvsr59/nvsr59_03.pdf.

The Future Forum proposes major changes to the government's plans for NHS reform

Integrated care should be given priority, with less emphasis on competition

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Competing interests: None declared.

Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2011;342:d3769
doi: 10.1136/bmj.d3769

The report of the Future Forum, established by the government to lead the listening exercise on the proposed reforms of the NHS in England, has put forward a series of recommendations for modifying the direction of these reforms and the Health and Social Care Bill currently before parliament.[1] Although it accepts the need for change, the forum has responded to the concerns of organisations representing patients, staff, and other stakeholders by reiterating the importance of the values contained in the NHS Constitution and urging caution about the role of competition in the NHS. It has stopped short of recommending that the Health and Social Care Bill should be abandoned, but the forum's proposals nevertheless amount to far reaching modifications of the government's plans.

The forum argues persuasively that care needs to be integrated around the needs of patients, noting that "concerns around integration came up time and time again" during the listening exercise. Citing examples of successful integration, including diabetes care in Bolton and care for older people in Torbay, it asserts that there is a need to move beyond arguing for integration to making it happen. Other recommendations in a short but wide ranging report include making patient choice a reality, allowing commissioning consortiums to take on their responsibilities only when they are ready to do so, and providing independent expert public health advice at all levels.

In advance of publication of the forum's report, the prime minister gave a clear indication that he was "ready for turning," to adapt Margaret Thatcher's memorable phrase. His speech at the National Hospital for Neurology

MARK THOMAS

Members of the Future Forum: Geoff Alltimes, Julie Moore, Steve Field, Kathy McLean, Stephen Bubb

and Neurosurgery on 7 June emphasised that competition would be used as a means and not an end, and that much more emphasis would be given to collaboration between healthcare providers and the integration of care.[2] He also argued that hospital doctors and nurses would be involved in advising on commissioning, anticipating one of the forum's recommendations. The government has accepted all of the core recommendations as a demonstration of its sincerity in launching the listening exercise and its willingness to take account of stakeholders' concerns.[3]

The fate of the reforms now hinges on coalition politics and the reaction of key groups of staff, especially general practitioners, as has been apparent since the reforms were first announced in the summer of 2010.[4] Although the forum's report provides a basis for the prime minister and the deputy prime minister to agree on changes to the Health and Social Care Bill and the general direction of reform, these changes have to be accepted by their supporters in parliament and the country. There are already signs of tension on this score as some Conservative members of parliament are unhappy at the reduced emphasis on the role of competition in healthcare. With Liberal Democrats claiming that the concessions they have negotiated amount to victory in the debate within government on reform, the future direction of health policy is not yet settled.

The reaction of general practitioners will also be important. The enthusiasm with which pathfinder commissioning consortiums have been established owes much to the willingness of a small proportion of general practitioners to pick up the gauntlet and lead their colleagues in taking on the responsibilities being offered to them. Proposed changes to the plans for consortiums, including the involvement of other clinicians and more formal requirements for governance, risk dissipating this enthusiasm if these general practitioners perceive that their freedoms and flexibilities are being fettered. It will be important to support consortiums that are able to take on responsibility for commissioning, so that they can do so as quickly as possible and avoid their commitment waning.

Equally important will be the ability of the NHS to absorb the increasing operational pressures it is facing while taking forward the much modified reforms. The prime minister's recent speech was notable less for what he had to say about these reforms than his commitments to keep waiting times low and maintain NHS spending in real terms. The very fact that he thought it necessary to make these commitments signifies concern at the heart of government that the NHS is struggling to sustain improvements in patients' access to care achieved under the last government. Seen in this context, the Liberal Democrats may have won only a pyrrhic victory on healthcare reform if the NHS is catapulted back into headlines as a result of declining performance.

Organisational changes and cuts in management costs made since the election have almost certainly contributed to the pressures facing the NHS, and their effects will continue to be felt even if the recommendations of the Future Forum are accepted. Modifying the pace of change in line with the forum's sensible advice may help alleviate the impact of these pressures, but the NHS still faces the biggest financial challenge in its history, as the all party Health Services Committee has pointed out.[5] In rising to this challenge, it is inevitable that changes will be made to how clinical services are organised, both to improve quality and patient safety and to release resources.

Politicians have been in denial since the election about the necessity for service reconfigurations, perhaps because of commitments made before the election and the well known difficulties of persuading the public to accept reduced geographical access to services, even if quality improves as a result. In an unscripted passage of his speech, the prime minister praised the improvements in stroke care brought about in London as a result of concentrating care in fewer hospitals, seemingly unaware that these improvements had resulted from the Healthcare for London programme that his government terminated soon after coming into office. The Future Forum makes only passing reference to service reconfigurations and yet they are crucial for the new model of care described in its report to be realised.

1 NHS Future Forum. Summary report on proposed changes to the NHS. TSSO, 2011. www.nationalvoices.org.uk/sites/www.nationalvoices.org.uk/files/Summary%20Report%20of%20the%20NHS%20Future%20Forum%20FINAL%20(2)_0.pdf.
2 Cameron D. Speech on the future of the NHS. 7 June 2011. www.number10.gov.uk/news/speeches-and-transcripts/2011/06/speech-on-the-nhs-64449.
3 Cameron D. PM's speech on the NHS. 14 June 2011. www.number10.gov.uk/news/speeches-and-transcripts/2011/06/pms-speech-on-the-nhs-2-64728.
4 Ham C. Why the plans to reform the NHS may never be implemented. *BMJ* 2010;341:c5032.
5 Health Select Committee. HC513-II. Third report—commissioning. 2011. www.parliament.uk/business/committees/committees-a-z/commons-select/health-committee/publications/.