RESEARCH

The *BMJ* is an Open Access journal. We set no word limits on *BMJ* research articles, but they are abridged for print. The full text of each *BMJ* research article is freely available on bmj.com

Scan this image with your smartphone to read our instructions for authors

11 **RESEARCH NEWS** All you need to read in the other general medical journals

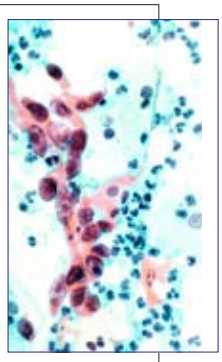
THIS WEEK'S RESEARCH QUESTIONS

14 How does the risk of cervical cancer in women with normal smears after histologically confirmed cervical intraepithelial neoplasia compare with that in women with a normal primary smear test result?

15 What is the cost effectiveness of human papillomavirus testing as a test of cure after treatment for cervical intraepithelial neoplasia?

16 What is the cost effectiveness of vaccinating people at high risk for invasive pneumococcal disease with the 13 valent pneumococcal conjugate vaccine?

17 Is melatonin effective in treating severe sleep problems in children with neurodevelopmental disorders?



WHAT OUR READERS ARE SAYING

Identifying the lowest effective dose of acetazolamide for the prophylaxis of acute mountain sickness

According to this meta-analysis published on 18 October [doi:10.1136/bmj.e6779], acetazolamide in doses of 250-750 mg daily are all more effective than placebo in preventing acute mountain sickness. Acetazolamide 250 mg daily is the lowest effective dose for which evidence is available, say the authors.

Here's what rapid respondent Matiram Pun said:

"Although I agree with the lowest effective dosage (250 mg/day in two divided dosages), the number of trials on the subject is limited…It is unclear if it works in all ranges of body mass index, especially in the higher ranges. An alternative way of looking into the efficacy of this lower dose would be to see if there is optimum physiological alteration in high altitude hypoxia. Is this low dose enough to facilitate hypoxic ventilator response or correct respiratory alkalosis?

Future research should test not only rapid ascent, a lower starting point, and lower doses of acetazolamide but also alternative medications. Not all individuals can tolerate acetazolamide because of its sulfonamide moiety. Furthermore, the populations who ascend to altitude are diverse—for example, people with comorbid conditions, elderly, mining workers, and pilgrims…Although alternatives to acetazolamide are not within the scope of the article, I was surprised to see gingko biloba as a first alternative, whereas non-steroidal anti-inflammatory drugs have recently been tested more frequently and found effective."

RESEARCH ONLINE: For new research articles see www.bmj.com/research

Podcasts

Listen to what you want, when you want, and how you want

Imagine waking up and automatically having the latest medical news, views, research, and education to listen to for free while you commute to work or exercise. This is the podcast listening experience.

Sign up at iTunes or download from bmj.com/multimedia/podcasts

BMJ

Risk of cervical cancer after completed post-treatment follow-up of cervical intraepithelial neoplasia: population based cohort study

Matejka Rebolj,[1 2] Theo Helmerhorst,[3] Dik Habbema,[1] Caspar Looman,[1] Rob Boer,[1] Joost van Rosmalen,[1] Marjolein van Ballegooijen[1]

EDITORIAL by Bleeker and colleagues
RESEARCH, p 15

[1]Department of Public Health, Erasmus MC, Rotterdam, Netherlands
[2]Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[3]Department of Obstetrics and Gynaecology, Erasmus MC, Rotterdam, Netherlands
Correspondence to: M Rebolj
mare@sund.ku.dk

Cite this as: *BMJ* 2012;345:e6855
doi: 10.1136/bmj.e6855

This is a summary of a paper that was published on bmj.com as *BMJ* 2012;345:e6855

bmj.com/podcasts
Listen to the authors of this paper discuss their research at http://bitly.com/UtJa6M

STUDY QUESTION

How does the risk of cervical cancer in women with complete follow-up after histologically confirmed cervical intraepithelial neoplasia compare with that in women with a normal primary smear test result?

SUMMARY ANSWER

After three or more consecutive normal smear test results following cervical intraepithelial neoplasia, the risk of cervical cancer was about four times higher than after a normal primary smear test result (35 per 100 000 woman years).

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The consistently observed excess risk of cervical cancer after treatment of cervical intraepithelial neoplasia cannot be fully explained by lack of follow-up.

Participants and setting

In the Netherlands, three consecutive normal smear test results are required after treatment of cervical intraepithel-ial neoplasia before a woman can return to routine five yearly screening. We identified from the Dutch nationwide network and register of histopathology and cytopathology (PALGA) all episodes with histologically confirmed cervical intraepithelial neoplasia grades 1 to 3, completed by three consecutive normal smear test results, and all normal primary smear test results.

Design, size, and duration

We counted woman years after 38 956 episodes of cervical intraepithelial neoplasia with completed follow-up and after 7 096 816 normal primary smear test results, until the next screening episode, diagnosis of cervical cancer, 31 December 2006, or after 10 years, whichever came first. The hazard ratio for cervical cancer, adjusted for year in follow-up, was calculated for periods after completed follow-up compared with periods after normal primary smear test results.

Main results and the role of chance

20 cases of cervical cancer were diagnosed during 56 956 woman years after completed follow-up of cervical intraepithelial neoplasia (35.1 per 100 000 woman years, 95% confidence interval 21.4 to 54.2). 1613 cases of cervical cancers were diagnosed during 25 020 697 woman years after normal primary smear test results (6.4 per 100 000 woman years, 6.1 to 6.8). The corresponding hazard ratio was 4.2 (95% confidence interval 2.7 to 6.5). The risk did not depend on the grade of cervical intraepithelial neoplasia.

Bias, confounding, and other reasons for caution

From PALGA, we were not able to determine how many women with histologically confirmed cervical intraepithelial neoplasia were treated. However, secondary data sources suggest that most Dutch women with grade 2 or 3 lesions, and about 40% of those with grade 1 lesions, must have been treated.

Generalisability to other populations

The contrast in the risk of cervical cancer would probably be larger if the Netherlands used shorter routine screening intervals. Furthermore, several countries recommend longer term post-treatment follow-up than the Netherlands. However, an extension of our study to smear tests beyond the third consecutive normal post-treatment test showed that the risk of cervical cancer remained higher (hazard ratio 3.6, 2.6 to 5.0) compared with normal primary smear test results without earlier abnormalities.

Study funding/potential competing interests

Funded by the Dutch National Institute for Public Health and the Environment (grant No 3022/07 DG MS/CvB/NvN). MR is currently involved in a comparative study of human papillomavirus tests, for which Roche Diagnostics, Genomica, Qiagen, and Gen-Probe provided assays and instrumentations. RB's institution received a grant from Health Insurance Executive Board. MvB was the principal investigator until 2008 on a project on the cost effectiveness of human papillomavirus vaccination, financed by GSK, a producer of human papillomavirus vaccines. There has been no collaboration with or support from pharmaceutical companies.

Hazard ratios of developing cervical cancer after three consecutive normal smear test results following histologically confirmed cervical intraepithelial neoplasia (CIN)

Exposure	Woman years at risk	Cases of cervical cancer	Hazard ratio* (95% CI)
CIN 1 (n=8837)	14 482	6	1.3 (0.4 to 3.7)
CIN 2 (n=9020)	13 752	6	1.4 (0.5 to 4.2)
CIN 3 (n=21 099)	28 722	8	1 (Reference)
Any CIN (n=38 956)	56 956	20	4.2 (2.7 to 6.5)
Normal primary smear test result (n=7 096 816)	25 020 697	1613	1 (Reference)

*Corrected for year in follow-up.

Cost effectiveness of human papillomavirus test of cure after treatment for cervical intraepithelial neoplasia in England: economic analysis from NHS Sentinel Sites Study

Rosa Legood,[1] Megan Smith,[2] Jie-Bin Lew,[2] Robert Walker,[2] Sue Moss,[3] Henry Kitchener,[4] Julietta Patnick,[5] Karen Canfell[2 6]

EDITORIAL by Bleeker and colleagues

RESEARCH, p 14

[1]Health Services Research and Policy Unit, London School of Hygiene and Tropical Medicine, London WC1 9HS, UK
[2]Cancer Research Division, Cancer Council NSW, Woolloomooloo, NSW 2011, Australia
[3]Centre for Cancer Prevention, Queen Mary University of London, Wolfson Institute of Preventive Medicine, London EC1M 6BQ
[4]School of Cancer and Enabling Sciences, University of Manchester, St Mary's Hospital, Manchester M13 9WL, UK
[5]NHS Cancer Screening Programme, Sheffield S10 3TH, UK
[6]School of Public Health, University of Sydney, Australia
Correspondence to:
R Legood
rosa.legood@lshtm.ac.uk

Cite this as: *BMJ* 2102;345:e7086
doi: 10.1136/bmj.e7086

This is a summary of a paper that was published on bmj.com as *BMJ* 2012;345:e7086

STUDY QUESTION To evaluate the cost effectiveness of human papillomavirus testing to determine management after treatment for cervical intraepithelial neoplasia.

SUMMARY ANSWER The human papillomavirus test of cure would be more effective and would be cost saving compared with cytology only follow-up.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Results of previous studies are inconsistent about whether human papillomavirus testing as a test of cure after treatment for cervical intraepithelial neoplasia is cost effective. If realistic assumptions are made about women's compliance with follow-up recommendations, human papillomavirus testing according to the protocol used in the NHS sentinel sites is likely to be more effective and cost less than strategies based on annual cytological follow-up of women treated for cervical intraepithelial neoplasia.

Main results

We simulated three alternative post-treatment management pathways: cytology only follow-up, the sentinel sites protocol (post-treatment follow-up incorporating human papillomavirus testing and cytology at six months), and an extended human papillomavirus follow-up protocol (post-treatment follow-up incorporating human papillomavirus testing and cytology at six and 12 months and cytology alone at 24 months). We found that the human papillomavirus test of cure according to the sentinel sites protocol was a more effective and less costly strategy than annual cytological follow-up over 10 years.

Design

We used a Markov modelling approach to combine cost and epidemiological data. We modelled costs and outcomes over a 10 year time horizon.

Source(s) of effectiveness

We used epidemiological data from the NHS Sentinel Sites Study and data from previous studies of post-treatment recurrence rates.

Data sources

Unit costs came from the NHS Sentinel Sites Study and national unit costs, projected over a 10 year horizon.

Results of sensitivity analysis

The findings were most sensitive to assumptions about the level of compliance with follow-up recommendations and the cost of collecting follow-up test samples. In the case of the sentinel sites protocol, the results were somewhat sensitive to the assumed characteristics of the human papillomavirus test.

Limitations

Data on the quality of life implications of alternative post-treatment management strategies were lacking.

Study funding/potential competing interests

The study was funded by the NHS Cancer Screening Programme. KC is involved in configuring a new trial of cervical screening in Australia which will involve support from several manufacturers.

Predicted outcomes over 10 years, per 1000 women treated

Recommended strategy	Cytology only follow-up	HPV test of cure—sentinel sites protocol	HPV test of cure—extended follow-up protocol
Health outcomes			
Residual underlying cases of CIN3+ at 10 years	29.1	20.7	21.5
Residual underlying cases of CIN3+ averted compared with current practice	—	8.4	7.6
Cost per additional underlying CIN3+ case averted at 10 years compared with current practice		−£1120 (cost saving)	£6474
Costs			
Discounted at 3.5% per year	£358 222	£348 834	£407 274

CIN=cervical intraepithelial neoplasia; HPV=human papillomavirus.

Vaccination of risk groups in England using the 13 valent pneumococcal conjugate vaccine: economic analysis

Mark H Rozenbaum,[1] Albert Jan van Hoek,[2] Douglas Fleming,[3] Caroline L Trotter,[4] Elizabeth Miller,[2] W John Edmunds[5]

[1]Unit of PharmacoEpidemiology and PharmacoEconomics, Department of Pharmacy, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, Netherlands
[2]Immunisation, Hepatitis and Blood Safety Department, Health Protection Agency, London, UK
[3]Birmingham Research Unit of the Royal College of General Practitioners, Birmingham, UK
[4]School of Social and Community Medicine, University of Bristol, Bristol, UK
[5]Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, London, UK
Correspondence to: M Rozenbaum
m.h.rozenbaum@rug.nl

Cite this as: *BMJ* 2012;345:e6879
doi: 10.1136/bmj.e6879

This is a summary of a paper that was published on bmj.com as *BMJ* 2012;345:e6879

bmj.com
Cost effectiveness of pneumococcal vaccination among Dutch infants (*BMJ* 2010;340:c2509)

STUDY QUESTION

What is the cost effectiveness of vaccinating people with high risk conditions for invasive pneumococcal disease with the 13 valent pneumococcal conjugate vaccine?

SUMMARY ANSWER

If the vaccine does not offer protection against non-bacteraemic pneumococcal pneumonia in high risk groups then it is unlikely that a targeted pneumococcal vaccination programme would be considered cost effective.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Despite the availability of the 23 valent polysaccharide pneumococcal vaccine, people with certain high risk conditions are still disproportionately affected by pneumococcal infections. The cost effectiveness of vaccinating high risk groups with the 13 valent pneumococcal conjugate vaccine depends on the timing of such a programme in relation to the introduction of infant immunisation with this vaccine and on how effective the vaccine is at protecting high risk people against non-bacteraemic pneumococcal pneumonia.

Main results

Increasing indirect protection resulting from the infant 13 valent pneumococcal conjugate vaccine programme means that the burden of disease preventable by targeting high risk groups will diminish in time. Under base case assumptions—that is, no overall impact on non-bacteraemic pneumonia in high risk groups and assuming the high risk vaccination programme would be launched two to three years after the infant programme—the incremental cost effectiveness ratio was estimated to be more than £30 000 (€37 216; $48 210) per quality adjusted life year gained for most risk groups.

Design

Economic evaluation using a cohort model to estimate the cost effectiveness of using the 13 valent pneumococcal conjugate vaccine from the perspective of healthcare providers.

Sources of effectiveness

A formal elicitation of expert opinion on vaccine related variables was carried out to construct a probability distribution that represents experts' knowledge and uncertainty.

Data sources

We used various data sources to populate our cost effectiveness analyses. These included laboratory data (Health Protection Agency) and the hospital episode statistics database for calculating the incidence of disease, case fatality ratios, serotype distributions, and share of meningitis and empyema. The Royal College of General Practitioners database was used for the calculation of the life expectancy of people with certain risk conditions. Costs were calculated by using software of the NHS healthcare resource group and the national schedule of reference costs for NHS trusts. Other assumptions were based on the scientific literature.

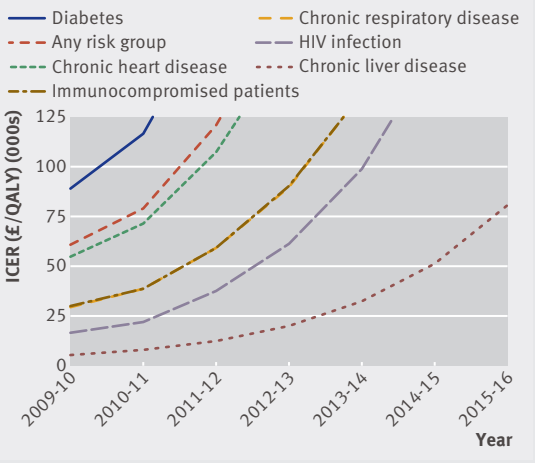
Results of sensitivity analysis

The sensitivity analysis showed that the results depend highly on the timing of the programme for high risk groups in relation to the introduction of infant immunisation with the 13 valent vaccine. This is because the infant programme is likely to reduce the incidence of vaccine type disease across all ages, including those in risk groups. Furthermore, the cost effectiveness also depended on how effective the vaccine is at protecting high risk people against non-bacteraemic pneumococcal pneumonia.

Limitations

Evidence for effectiveness against non-bacteraemic pneumococcal pneumonia is weak at present, although a large scale clinical trial is currently underway that should shed light on this.

Incremental cost effectiveness ratio (ICER) of vaccinating risk groups with 13 valent pneumococcal conjugate vaccine



Study funding /potential competing interests

MHR was employed by the University of Groningen while doing this study. In 2011, he joined Pfizer Netherlands. Pfizer had no involvement in the development of the model or any influence on the results, outcomes, and conclusions drawn or in the preparation of this paper. AJvH and JE were supported by the UK Department of Health Policy Research Programme (grant No 039/0031). The funder had no part in the design or execution of the study or the analysis and interpretation of the results. The views expressed here are those of the authors and not necessarily those of the Department of Health.

Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial

P Gringras,[1] C Gamble,[2] A P Jones,[2] L Wiggs,[3] P R Williamson,[2] A Sutcliffe,[4] P Montgomery,[5] W P Whitehouse,[6] I Choonara,[7] T Allport,[8] A Edmond,[8] R Appleton,[9] on behalf of the MENDS Study Group

EDITORIAL by Lerchi and Reiter

[1]King's College London and Evelina Children's Hospital, St Thomas' Hospital, London SE1 7EH, UK
[2]Medicines for Children Research Network Clinical Trials Unit, University of Liverpool, Alder Hey Children's NHS Foundation Trust, Liverpool L12 2AP, UK
[3]Department of Psychology, Oxford Brookes University, Headington, Oxford OX3 0BP, UK
[4]GAP Unit, Institute of Child Health, UCL, London WC1N 1EH
[5]Centre for Evidence-Based Intervention, University of Oxford, Barnett House, Oxford OX1 2ER
[6]University of Nottingham and Nottingham Children's Hospital, Nottingham University Hospitals NHS Trust, Nottingham
[7]Academic Division of Child Health, Medical School, Derbyshire Children's Hospital, Derby DE22 3DT, UK
[8]Centre for Child and Adolescent Health, Oakfield House, University of Bristol, Bristol BS8 2BN, UK
[9]Roald Dahl EEG Department, Paediatric Neurosciences Foundation, Alder Hey Children's NHS Foundation Trust, Liverpool
Correspondence to: P Gringras
Paul.Gringras@gstt.nhs.uk

Cite this as: *BMJ* 2012;345:e6664
doi: 10.1136/bmj.e6664

This is a summary of a paper that was published on bmj.com as *BMJ* 2012;345:e6664

bmj.com

Research: Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction (*BMJ* 2006;332:385

STUDY QUESTION

Is melatonin effective and tolerable in treating severe sleep problems in children with neurodevelopmental disorders?

SUMMARY ANSWER

Children fell asleep significantly faster but woke earlier and gained little additional sleep on melatonin.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Melatonin is widely prescribed within this population with inconsistent conclusions about its effectiveness. This study shows that children given an instant release preparation of melatonin fall asleep earlier but also wake earlier. Doses as low as low as 0.5 mg might be effective.

Design

This was a randomised, parallel group, double masked, multicentre, placebo controlled, phase III trial. At registration, parents/carers were provided with an advice booklet on standardised sleep behaviour therapy for a one month run-in period. Randomisation lists were generated with a 1:1 ratio with block randomisation. At randomisation, each child was given 0.5 mg immediate release melatonin or placebo. Every four weeks, we reviewed the child's sleep pattern and increased drug dose according to required criteria. There was a maximum of three dose increments from 0.5 mg to 2 mg, 6 mg, and a maximum of 12 mg.

Participants and setting

Participants were 146 children aged 3 years to 15 years 8 months referred by community paediatricians to 19 hospitals across England and Wales. They had a range of neurological and developmental disorders and a severe sleep problem.

Primary outcome

Total night time sleep after 12 weeks, adjusted for baseline recorded in sleep diaries completed by parents. Secondary outcomes included sleep onset latency, child behaviour, family functioning, and adverse events. Sleep was measured subjectively by parental sleep diaries and objectively by actigraphy.

Main results and the role of chance

Melatonin increased total sleep time by 22.4 minutes (95% confidence interval 0.5 to 44.3; P=0.04) measured by sleep diaries (n=110) and 13.3 minutes (−15.4 to 42.2; P=0.36) measured by actigraphy (n=59). Melatonin reduced sleep onset latency measured by sleep diaries (−37.5 minutes, −55.3 to −19.7; P<0.001) and actigraphy (−45.3 minutes, −68.8 to −21.9; P<0.001). Melatonin was most effective for children with the longest sleep latency (P=0.009) and resulted in earlier waking times than placebo (29.9 minutes, 13.6 to 46.3). Child behaviour and family functioning outcomes favoured melatonin but were not significant.

Harms

Adverse effects were few, mild in degree, and distributed equally between the two groups with no increase in, or new onset of, epileptic seizures.

Bias, confounding, and other reasons for caution

The objective sleep data were based on the use of acti-graphy, but the percentage of missing data was high, with data available only for those children who could tolerate the actigraphy equipment (actiwatch). Some missing data relevant for the primary outcome were missing, but the conclusions were robust to sensitivity analyses. The definition of sleep disorder did not vary across the age range of children.

Generalisability to other populations

The wide inclusion study criteria of all children with neurodevelopmental delay maximises generalisability of results to everyday clinical practice.

Study funding/potential competing interests

The study was supported through the NIHR Health Technology Programme (project No 05/14/02), through the Medicines for Children Research Network and local research networks. Active drugs and placebo were manufactured by Penn Pharmaceuticals and funded by Alliance Pharma. This report presents independent research commissioned by the National Institute for Health Research (NIHR). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), the Health Technology Assessment (HTA) programme, or the Department of Health.

Trial registration number

ISRCT No 05534585.

Primary and secondary sleep outcomes in study of effect of melatonin on sleep problems in children with neurodevelopmental disorders. Figures are means (SD)

	Melatonin		Placebo		
	No of children	Change	No of children	Change	Adjusted difference
Sleep diary					
Total sleep (min)	51	40.5 (71.8)	59	12.5 (52.5)	22.43 (0.5 to 44.3)*
Sleep onset latency (min)	54	−47.2 (64.4)	59	−9.7 (49.6)	−37.5 (−55.3 to −19.7)†
Actigraphy					
Total sleep (min)	30	15.7 (63.6)	29	8.3 (52.0)	13.3 (−15.5 to 42.2)
Sleep onset latency (min)	24	−58.3 (53.7)	25	−3.71 (47.8)	−45.3 (−68.8 to −21.9)†
Sleep efficiency‡ (%)	30	4.81 (9.8)	28	1.56 (9.5)	4.03 (−0.6 to 8.7)

*P<0.05.
†P<0.001.
‡(No of minutes spent sleeping in bed/total No of minutes spent in bed)×100.