

THIS WEEK'S RESEARCH QUESTIONS

- 677** What are the differences in the effectiveness and cost effectiveness of bivalent and quadrivalent human papillomavirus vaccination?
678 How well have men who have sex with men complied with the UK blood services' lifetime ban on blood donation?
679 Is consumption of chocolate associated with reduced risk of cardiometabolic disorders?
680 How random and costly are processes used to choose research projects for funding in Australia?

Should the UK switch to the quadrivalent human papillomavirus vaccination?

Vaccination against human papillomavirus among teenage girls to prevent cervical cancer has been in the news recently, for all the wrong reasons. Minnesota congresswoman and US presidential republican candidate Michele Bachmann told NBC on 13 September that “[a mother] told me that her little daughter took that vaccine, and she suffered from mental retardation thereafter. It can have very dangerous side effects (<http://wapo.st/nTlvNh>).” The American Academy of Pediatrics quickly retorted that “there is absolutely no scientific validity to this statement. Since the vaccine has been introduced, more than 35 million doses have been administered, and it has an excellent safety record (<http://bit.ly/pNXb0p>)” and bioethicist Arthur C Caplan from the University of Pennsylvania bet \$10 000 (for charity) that Bachmann could not prove her claim (<http://n.pr/n15hff>).

In the UK at least 4.5 million doses of the bivalent vaccine have been given safely to girls aged 12-13 (<http://bit.ly/mPgZbd>). With the MHRA's decision to choose the bivalent vaccine due for review, is it time to switch to the quadrivalent vaccine? Mark Jit and

colleagues' 2008 economic evaluation in the *BMJ* found the quadrivalent vaccine to be cost effective, but noted that “a bivalent vaccine with the same efficacy against human papillomavirus types 16 and 18... may be as cost effective... although less effective as it does not prevent anogenital warts (*BMJ* 2008; 337:a769).” Now the same research team has modelled the latest data on effectiveness and safety (p 677). In a nuanced analysis with considerable uncertainty, the authors conclude that the quadrivalent vaccine is still more cost effective if the two are equally priced.

Blood donation by men who have sex with men



On September 8, the health ministers of England, Wales, and Scotland agreed to a change in the criteria that prevent men who have had sex with men from donating blood, from the current lifetime ban to a deferral period of one year after having sex with a man. In a timely qualitative study, P Grenfell and colleagues interviewed men who had sex with men about donation, finding that 11% had given blood despite being ineligible under the lifetime ban, and that a change in the rules was likely to be welcomed as “a step in the right direction” (p 678).

Some media responses to the announcement, however, declared that the new rules will remain discriminatory and would only slightly expand the pool of eligible donors (<http://bit.ly/q15ofC>). Matthew Sothorn echoed these views (*BMJ* 2011;343:d5793), adding that the changes still fail to address risky behaviour among heterosexual donors. And later in the month, the Liberal Democrat party called for the policy to be updated further (<http://bit.ly/ns3p7k>).

A more detailed questionnaire about individual behaviour for all potential donors has been proposed as a better way to determine risk, although editorialist Jay Brooks notes that this could be impractical. He also observes that the new criteria will need to be thoughtfully communicated, in light of the study's finding that many men misunderstood the current donation policy—which was a major reason for non-compliance. To the dismay of gay rights supporters, the lifetime ban will continue to apply in Northern Ireland (<http://bit.ly/oMC7yW>).

Chocolate and cardiometabolic disorders

After all the media attention this study received (just try Googling “chocolate” and “*BMJ*,” and you'll soon get the gist), anything written here is likely to be superfluous. Suffice it to say that this meta-analysis by Adriana Buitrago-Lopez and colleagues (p 679) included only seven observational studies with large variation in measurement, methods, and outcomes evaluated, so the results are tentative and show only association; however, that association is pretty impressive (high chocolate consumption linked with a decrease of a third in the risk of cardiometabolic disorders).

Certainly, Johan Mackenbach seems quite taken with the study in his linked editorial (p 649), and he summarises the situation nicely: “If this represents a causal effect it is substantial and comparable in magnitude to that of several other lifestyle related determinants of cardiovascular disease, such as serum lipids.”

One point that the paper mentions, but that many media stories overlooked, is that if chocolate ever does get “weaponised” to be a clinical treatment, the sugar and fat content will almost certainly need to be reduced—which is going to make it taste a lot less like chocolate and a lot more like medicine.



Comparing bivalent and quadrivalent human papillomavirus vaccines: economic evaluation based on transmission model

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EDITORIAL by Verheijen

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News: Study shows HPV home testing could improve cervical screening uptake (*BMJ* 2011;342:d1734)

Editorial: Monitoring HPV vaccination programmes (*BMJ* 2010;340:c1666)

Editorial: Should HPV vaccine be given to men? (*BMJ* 2009;339:b4127)

STUDY QUESTION

What are the differences in the effect and cost effectiveness of bivalent and quadrivalent human papillomavirus (HPV) vaccination?

SUMMARY ANSWER

The bivalent vaccine needs to be cheaper than the quadrivalent vaccine to be equally cost effective, mainly because of its lack of protection against anogenital warts.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The two licensed HPV vaccines both protect against HPV types 16 and 18 (which cause most cases of cervical cancer) but differ in terms of licensure indications, protection against disease due to other HPV types, and reported long term immunogenicity. Even when possible longer duration of protection and better cross protection against non-vaccine HPV types of the bivalent vaccine are taken into consideration, the quadrivalent vaccine is still more cost effective if the two are equally priced.

Main results

The quadrivalent vaccine may have an advantage in reducing healthcare costs and quality adjusted life years

(QALYs) lost, mainly because of the protection it confers against anogenital warts. The bivalent vaccine may have an advantage in preventing death due to cancer.

Design

Economic evaluation based on transmission model.

Source(s) of effectiveness

Vaccine trials, including recent evidence differentiating the two vaccines in terms of long-term follow-up of vaccinated cohorts as well as protection against genital warts, non-vaccine HPV types, and non-cervical diseases related to HPV infection.

Data sources

Published surveillance and epidemiological studies.

Results of sensitivity analysis

The figure shows the additional cost per dose for the quadrivalent vaccine that makes it equally cost effective as the bivalent vaccine under different scenarios about vaccine characteristics, and with one QALY valued at either £20 000 or £30 000. The additional price that can be charged for the quadrivalent vaccine ranges from £19 to £38 if one QALY is valued at £30 000 and both vaccines can prevent all types of HPV related cancers (scenarios 7–12 in figure). If the vaccines are assumed to protect only against the cancer end points listed in their licensure (scenarios 1–6), then the differential between threshold costs per dose for the two vaccines is greater (medians of £48 to £68) because of the additional protection given only by the quadrivalent vaccine against vulvar, vaginal, and anal cancers.

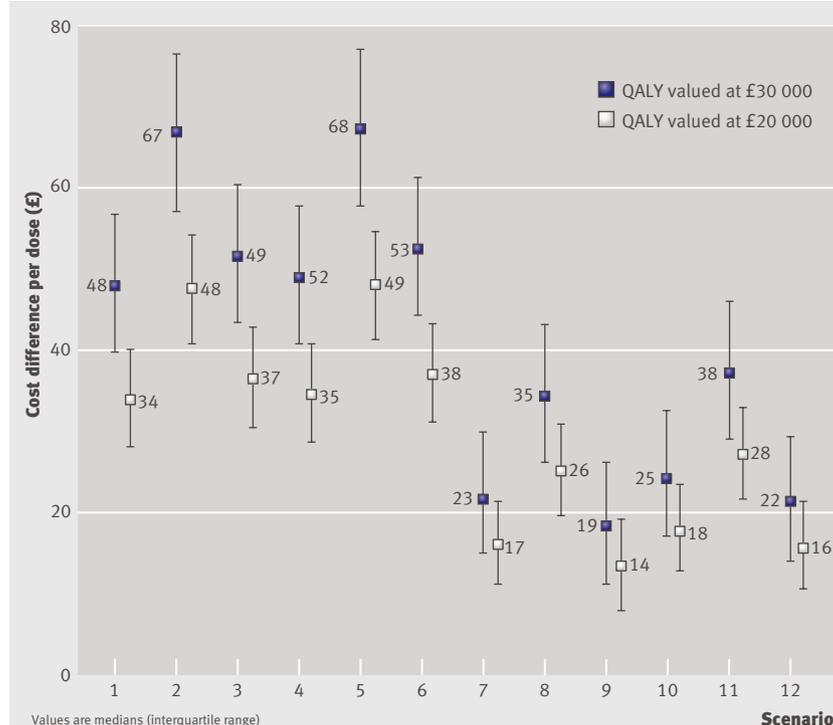
Limitations

It is not clear how differences in vaccine composition, licensed end points, immunogenicity, and cross protection may affect clinical effectiveness at the population level. Only poor data are available on the natural course of HPV related cancers in sites other than the cervix. Simplifications were made to the way non-vaccine HPV types and recurrent respiratory papillomatosis were modelled because of data limitations.

Study funding/potential competing interests

RC was funded by a grant from the Policy Research Programme of the Department of Health, England. OH was funded by a Medical Research Council Clinical Research Training Fellowship. OH has received unrestricted funding from Sanofi Pasteur to investigate quadrivalent L1 vaccines as a therapy for recurrent respiratory papillomatosis.

ADDITIONAL COST PER DOSE OF QUADRIVALENT VACCINE TO MAKE BIVALENT VACCINE EQUALLY COST EFFECTIVE



Views and experiences of men who have sex with men on the ban on blood donation: a cross sectional survey with qualitative interviews

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EDITORIAL by Brooks

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News: UK lifts lifetime ban on gay men giving blood (*BMJ* 2011;343:d5765)

Head to Head: Should men who have ever had sex with men be allowed to give blood? (*BMJ* 2009;338:b311)

Feature: Bad blood: gay men and blood donation (*BMJ* 2009;338:b779)

Personal View: The blood service should ask donors about practice, not just partners (*BMJ* 2011;343:d5793)

bmj.com/podcast

It's all in the blood

STUDY QUESTION

What is the level of compliance with the UK blood services' exclusion of men who have had penetrative sex with a man from ever donating blood, and how might a revised rule best be communicated and implemented?

SUMMARY ANSWER

11% of men with experience of male penetrative sex reported having donated blood in Britain while ineligible and a one year deferral was considered preferable to the current lifetime exclusion.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Improved blood screening techniques and epidemiological knowledge have prompted reconsideration of the lifetime ban on blood donation by men who have sex with men. Such men preferred a one year blood donor deferral on the basis of perceived rationality and equity.

Participants and setting

Of 32 373 men in a general population sample, questions were asked of men reporting male sexual contact (n=1028), and of a general population subsample (n=3914). In depth interviews were conducted with 30 "compliers" and "non-compliers" with the UK blood services' "MSM donor deferral"—the lifetime ban on blood donation by men who had ever had penetrative (oral or anal) sex with a man.

Design

A random location, cross sectional survey followed by qualitative, in depth interviews.

Primary outcomes

Compliance with the "MSM donor deferral" among men who had had penetrative sex with a man, and their views on and experiences of donating blood.

Main results and the role of chance

Of the 474 male survey respondents who reported experience of male penetrative sex, 50 (11%) had donated blood in Britain since becoming ineligible under the MSM donor deferral ("non-compliers") and 11 (2%) had donated in the previous year. Ineligible donation was less common (P<0.01) among men who had had male penetrative sex in the past 12 months than among men who last did so longer ago.

Reasons for non-compliance included self categorisation as low risk, discounting the sexual experience that barred donation, belief in the infallibility of blood screening, concerns about confidentiality, and misunderstanding or perceived inequity of the rule. Participants considered a one year deferral since last male penetrative sex to be generally feasible, equitable, and acceptable, but highlighted the need for clear communication of a revision and its rationale.

Bias, confounding, and other reasons for caution

The prevalence of reported male sexual experience in our study (3%) was considerably lower than that found in a dedicated national survey of sexual behaviour in 2000 (8%), possibly reflecting differences in methodology and age range.

Study funding/potential competing interests

The study was funded by the Department of Health. WN worked for Terrence Higgins Trust until 2009 and undertakes consultancy work for it. KS is employed by the UK Health Protection Agency.

BLOOD DONATION PRACTICE AMONG MEN REPORTING MALE SEXUAL CONTACT

Donation practice	Men with experience of male penetrative sex			Men with experience of non-penetrative male sex only	All#
	In past 12 months	Before past 12 months only	Any†		
Ever donated blood in England, Wales, or Scotland	57/256 (22%)	69/227 (30%)	126/485 (26%)	164/521 (31%)	295/1006 (29%)
Ever donated blood despite ineligibility§	17/249 (7%)**	33/219 (15%)**	50/474 (11%)	—	—
Donated in past 12 months¶	5/238 (2%)	6/212 (3%)	11/456 (3%)	16/475 (3%)	27/946 (3%)
Reasons for not donating blood:	(n=190)	(n=153)	(n=348)	(n=349)	(n=707)
Excluded because of male penetrative sex	46 (24%)	15 (10%)	61 (18%)**	4 (1%)**	66 (9%)
Excluded because of other male sexual contact	36 (19%)	13 (8%)	49 (14%)**	2 (1%)**	51 (7%)
Excluded for other reasons	12 (6%)	9 (6%)	23 (7%)	36 (10%)	59 (8%)
Medical reasons (such as anaemia)	12 (6%)	15 (10%)	27 (8%)	34 (10%)	61 (9%)
Never considered it	26 (13%)	38 (25%)	64 (18%)*	88 (25%)*	157 (22%)
Do not want to	23 (12%)	10 (7%)	33 (9%)	43 (12%)	78 (11%)
Considered it but not got around to it	21 (11%)	26 (17%)	49 (14%)**	83 (24%)**	133 (19%)
Too busy	12 (6%)	16 (10%)	29 (8%)	41 (12%)	70 (10%)
Fear of needles or pain	18 (9%)	25 (16%)	43 (12%)	38 (11%)	81 (11%)

*P<0.05, **P<0.01 (comparing those with or without experience of penetrative sex, or how recent the experience was for ineligible donation).

†Includes non-response about how recent the experience was.

‡Includes non-response with regard to experience of male penetrative sex.

§Ever donated blood since first penetrative sex with a man and since MSM donor deferral (1986 or later).

¶Numerators are an estimate, reported to nearest integer, based on "year of last donation" and "interview week."

Chocolate consumption and cardiometabolic disorders: systematic review and meta-analysis

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Letter: Chocolate and blood pressure: Chocolate dose may be too much
(*BMJ* 2010;341:c4176)

bmj.com/podcasts

Oscar Franco talks about his linked meta-analysis

STUDY QUESTION

Is chocolate consumption associated with reduced risk of cardiometabolic disorders?

SUMMARY ANSWER

Yes, high levels of chocolate consumption are associated with about a one third reduction in the relative risk of cardiometabolic disorders.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Cocoa and chocolate are thought to have antihypertensive, anti-inflammatory, anti-atherogenic, and antithrombotic effects. Increased chocolate intake is significantly associated with a reduced risk of cardiovascular disease.

Selection criteria for studies

We searched Medline, Embase, Cochrane Library, PubMed, CINAHL, IPA, Web of Science, Scopus, and Pascal to October 2010 for randomised trials and cohort, case-control, and cross sectional studies conducted in human adults of associations between different levels of chocolate consumption and the risk of cardiometabolic disorders. We also searched the reference lists of retrieved articles for further publications and contacted the authors of retrieved papers for any unpublished studies.

Primary outcome(s)

Relevant cardiometabolic disorders were cardiovascular disease, myocardial infarction, stroke, ischaemic heart disease, heart failure, diabetes, and metabolic syndrome.

Main results and role of chance

Seven studies, which included 114 009 participants, were included in our analysis—one a cross sectional study from the United States, and six cohort studies carried out in Europe, Japan, and North America with a range of time to follow-up of 8–16 years. No study reported on metabolic syndrome, but four studies measured more than one outcome. These outcomes were assessed separately in the analysis, giving a total of 13 measures of association (two each for diabetes, coronary heart disease, cardiovascular disease, myocardial infarction, and heart failure, and three for stroke). All the studies reported chocolate consumption in a different manner, and, because of this heterogeneity, we compared the lowest and highest categories of consumption in each study to measure the association of chocolate intake with outcomes. All the measures of association reported were adjusted for age and several other variables, including sex, body mass index, physical activity, smoking, dietary factors (including coffee consumption), education, and drug use.

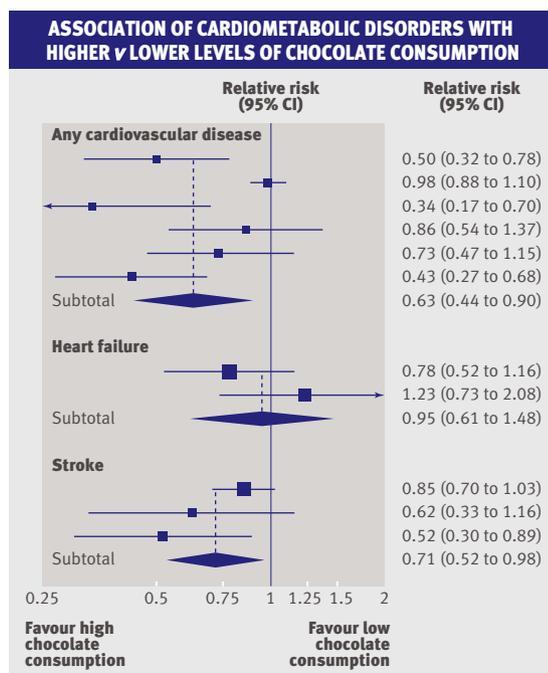
On pooling the retrieved measures of association, we found that high chocolate consumption was associated with about a one third decrease in the risk of cardiometabolic disorders—37% in the case of any cardiovascular disease (relative risk 0.63 (95% confidence interval 0.44 to 0.90)) and 29% in the case of stroke (0.71 (0.52 to 0.98)) (see figure). No significant association was observed in relation to heart failure (relative risk 0.95 (0.61 to 1.48)). Only one study evaluated diabetes, and it reported a beneficial association with high chocolate consumption in Japanese men and women (hazard ratios 0.65 (0.43 to 0.97) and 0.73 (0.48 to 1.13) respectively).

Bias, confounding, and other reasons for caution

Limited information was available with substantial heterogeneity observed between studies, indicating the need for further studies, more detailed reporting on the level of chocolate consumption, and the corroboration of observational findings with experimental studies.

Study funding/potential competing interests

This study received no specific funding, and the authors have no competing interests.



Funding grant proposals for scientific research: retrospective analysis of scores by members of grant review panel

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STUDY QUESTION

What are the randomness and costs arising from processes used to choose health and medical research projects for funding in Australia?

SUMMARY ANSWER

Allocating funding is costly and somewhat random and estimating random variability in panel members' scores showed that 59% of 620 funded proposals could be funded or not funded owing to such randomness.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Health and medical research aims to progress evidence based medicine but decisions about which research proposals to fund are not grounded in evidence. Decisions about funding health and medical research are somewhat random and applicants bear the most costs, which arise from the time required to participate.

Participants and setting

We evaluated all grant review panel members' scores for 2705 proposals submitted in 2009 to the National Health and Medical Research Council of Australia.

Design, size, and duration

A statistical bootstrap procedure was used to estimate variability in scores for each grant proposal. We examined how this scoring variability translated into variability in ranks and hence funding decisions. For each grant we estimated its minimum and maximum rank. This revealed whether a grant was always, sometimes, or never above the funding line after accounting for the randomness in the review process. We estimated the costs of panels with seven, nine, or 11 members, and coupled these with information about the number of grants effectively funded to estimate the incremental cost per grant effectively funded from larger panels.

Main results and the role of chance

The figure shows the best and worst performing panels of 45 grant review panels; the rank for the grant proposal marked with an asterisk ranged from the fifth best to the worst. Overall only 9% (n=255) of the 2705 grants were always above the funding line, 61% (n=1662) were never above the funding line, and 29% (n=788) were sometimes above and sometimes below the funding line. Reliability can be increased by using the most effective system of 11 panel members and is probably worth while as the extra cost per extra grant effectively funded is \$A18 541 (£11 848; €13 482; \$19 343), only 3% of the average grant value awarded.

Bias, confounding, and other reasons for caution

The scores of panel members are unlikely to be independent. This study only considered variation due to panel members' scores in relation to the funding line. If two independent panels assessed the same grants then variability might be higher. The costs of preparing grants were elicited from a small sample of researchers based at two institutions, and a nationally representative sample would more accurately reflect costs.

Generalisability to other populations

Very strong and weak grant proposals should be identified consistently, but many proposals will occupy a tightly packed middle ground. These proposals are the most difficult to separate and a slight change in score can push a proposal below or above a funding line. Any grant assessment process is likely to encounter this problem, especially the very competitive schemes with large numbers of applications.

Study funding/potential competing interests

This study received no funding and we have no competing interests.

