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RESEARCH

Public health impact and cost effectiveness of mass vaccination with live attenuated human rotavirus vaccine (RIX4414) in India: model based analysis

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EDITORIAL by Griffiths et al

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ABSTRACT

Objectives To examine the public health impact of mass vaccination with live attenuated human rotavirus vaccine (RIX4414) in a birth cohort in India, and to estimate the cost effectiveness and affordability of such a programme.

Design Decision analytical Markov model encompassing all direct medical costs. Infection risk and severity depended on age, number of previous infections, and vaccination history; probabilities of use of inpatient and outpatient health services depended on symptom severity.

Data sources Published clinical, epidemiological, and economic data. When possible, parameter estimates were based on data specific for India.

Population Simulated Indian birth cohort followed for five years.

Main outcome measures Decrease in rotavirus gastroenteritis episodes (non-severe and severe), deaths, outpatient visits, and admission to hospital; incremental cost effectiveness ratio of vaccination expressed as net cost in 2007 rupees per life year saved.

Results In the base case, vaccination prevented 28 943 (29.7%) symptomatic episodes, 6981 (38.2%) severe episodes, 164 deaths (41.0%), 7178 (33.3%) outpatient visits, and 812 (34.3%) admissions to hospital per 100 000 children. Vaccination cost 8023 rupees (about £100, €113, $165) per life year saved, less than India's per capita gross domestic product, a common criterion for cost effectiveness. The net programme cost would be equivalent to 11.6% of the 2006-7 budget of the Indian Department of Health and Family Welfare. Model results were most sensitive to variations in access to outpatient care for those with severe symptoms. If this parameter was increased to its upper limit, the incremental cost effectiveness ratio for vaccination still fell between one and three times the per capita gross domestic product, meeting the World Health Organization's criterion for "cost effective" interventions. Uncertainty analysis indicated a 94.7% probability that vaccination would be cost effective according to a criterion of one times per capita gross domestic product per life year saved, and a 97.8% probability that it would be cost effective according to a criterion of three times per capita gross domestic product.

Conclusions Across a wide range of assumptions, mass RIX4414 vaccination in India would probably prevent substantial morbidity and mortality at a cost per life year saved below typical thresholds of cost effectiveness. The opportunity costs of such a programme in this or similar settings, however, should be weighed up carefully.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Nearly a quarter of deaths from rotavirus gastroenteritis occurs in India, a country with a high degree of rotavirus strain diversity, limited access to health care, and tightly constrained financial resources.

WHO has recently recommended rotavirus vaccination in developing countries of Asia and Africa

WHAT THIS STUDY ADDS

A model based on India specific inputs where possible, showed a 29.7% reduction in symptomatic episodes, 41.0% reduction in rotavirus mortality, 33.3% reduction in outpatient visits, and 34.3% reduction in hospital admissions with a programme of vaccination with RIX4414

A vaccination programme would satisfy standard criteria for cost effectiveness across a wide range of assumptions—including lower than expected vaccine efficacy—albeit at a substantial net programme cost

INTRODUCTION

Studies of two new oral rotavirus vaccines are ongoing in several developing Asian and African countries and reporting of these data is expected to begin later in 2009.[1] Based on preliminary results, the World Health Organization has recently recommend inclusion of rotavirus vaccination in these countries' national immunisation programmes.[2] The current generation of rotavirus vaccines costs substantially more than traditional childhood vaccines given in these countries.[1]

We estimated the public health impact of mass vaccination for a birth cohort in India and examined the incremental cost effectiveness and affordability of such a programme. We focused on live attenuated human rotavirus vaccine—also known as RIX4414—because of the more diverse population in which its efficacy has been tested and a full course of RIX4414 requires only two doses compared with the three required for the alternative pentavalent vaccine.[3]

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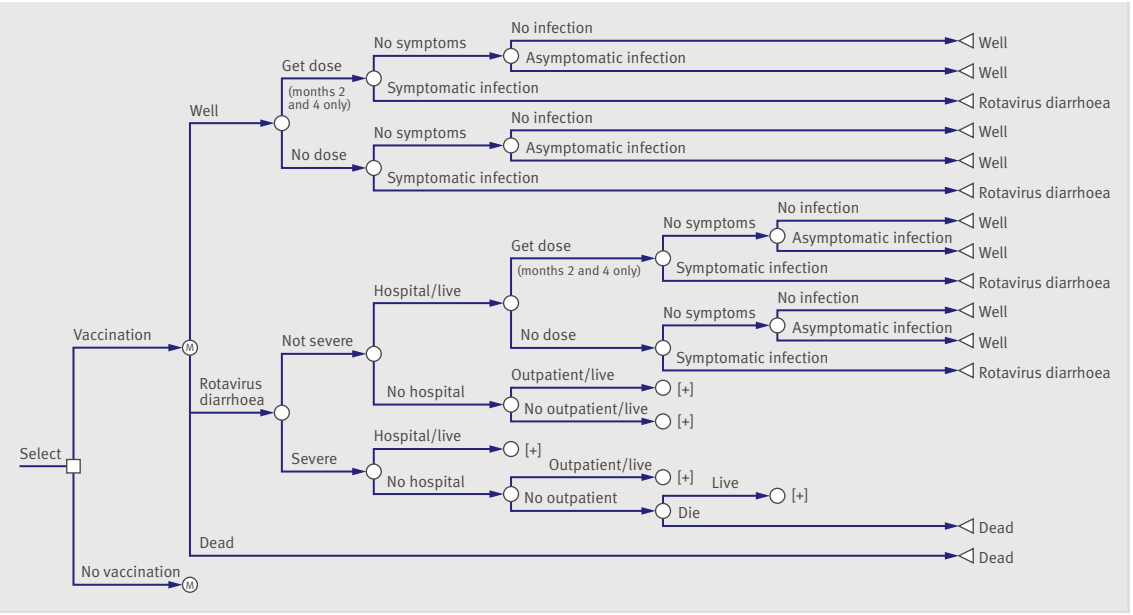

Fig 1 | Schematic of Markov model. Each individual begins life in the well state and thereafter resides in either the well, symptomatic, or dead state during each one month cycle for a total of 60 cycles. Individuals can receive doses of live attenuated human rotavirus vaccine at months two and four only. At the end of each cycle, each individual's risk for rotavirus infection is determined by number of vaccine doses received, time since receiving most recent dose, and number of previous rotavirus infections. If infected, individuals might develop symptoms in which case they will begin the next cycle in symptomatic state. In symptomatic state, gastroenteritis can be non-severe (Vesikari score <11) or severe (Vesikari score ≥11). Symptom severity dictates probability that each individual will receive hospital care, outpatient care, or no formal treatment. Those with severe disease who receive no formal treatment are at risk for death. Each month, there is an age dependent background risk of death from non-rotavirus causes (not shown). M in circle represents Markov node; branches emanating from a Markov node represent possible states of being. Open circle represents chance node; branches emanating to right represent possible outcomes of probabilistic process. Left pointing triangle (◁) designates terminal node; here, the state in which next cycle should begin is given. [+] signifies that portion of tree has been collapsed because it replicates portion already shown. "Get dose" signifies contingency that individual receives dose of vaccine, "no dose" signifies that they do not

METHODS

Model overview

We developed an individual based Markov model, which we analysed using Monte Carlo microsimulation methods. The base case evaluates only direct medical costs, including those incurred by patients' families or by any public sector entity contributing toward the cost of care. In a secondary analysis from the societal perspective, we also included direct non-medical costs such as transportation expenses for patients' families and indirect costs such as foregone wages of parents caring for sick children. The model's time horizon consisted of 60 one month cycles. We assumed that administration of the vaccine would be piggybacked on the existing WHO expanded programme on immunisation and given concomitantly with other routine vaccinations, including oral polio vaccine. Possible states of individuals in the model were well, rotavirus diarrhoea, and dead (fig 1).

Each possible chance event in the model was associated with an evidence based probability and the exact sequence and timing of events experienced by a given individual were the results of random number draws occurring at each juncture of the model. We aggregated the experience of 200 000 simulated individuals to predict the expected number of rotavirus infections (up to three per individual); their severity; the number of admissions to hospital, clinic visits, and home treatments for rotavirus gastroenteritis; the total cost of rotavirus related use; and the number of rotavirus related deaths under two different strategies: universal vaccination with RIX4414 at the recommended ages of 2 and 4 months[4] versus no vaccination (the status quo).

Incidence, morbidity, and mortality

Rates of rotavirus infection (but not outcomes of infection) are similar worldwide.[5] Accordingly, we based parameters related to infection risk on a rigorous prospective study of rotavirus incidence among a cohort of 200 Mexican infants followed from birth to 24 months of age.[6] See bmj.com.

Consistent with recent experience in India, individuals receiving formal medical attention faced no risk of death from rotavirus, irrespective of the severity of gastroenteritis. We determined the model parameter representing probability of death for those with severe rotavirus gastroenteritis who did not receive formal medical attention by using a simple calibration technique. We varied the parameter systematically until the model produced a five year risk of rotavirus mortality in the no vaccination group that matched observed rotavirus mortality in India (one in 250 children[7]). We did not explicitly

incorporate any additional survival benefit from home oral rehydration. Within each cycle all individuals also faced an age dependent probability of death from non-rotavirus causes based on published Indian life tables.[8]

Vaccine characteristics

We assumed that coverage rates for doses one and two of the vaccine would match rates for doses one and three of the diphtheria-tetanus-pertussis vaccine in India. Using a previously validated technique,[9] we estimated setting specific efficacy based on serotype specific efficacy data and combined prevalence figures from northern, eastern, and southern India. See bmj.com. We assumed no risk of serious adverse events for those receiving the vaccine.[10]

Probabilities related to use of health services

We estimated severity dependent probabilities of use of inpatient and also outpatient services. We assumed that the proportion of outpatients whose symptoms were severe would be half that of inpatients.[11] We estimated the probability of admission given severe infection as 9.7%, the probability of admission given non-severe infection as 0.72%, the probability of outpatient treatment given severe infection as 57.5%, and the probability of outpatient treatment given non-severe infection as 14.1%. Those not receiving any formal medical treatment were considered to have been treated at home by the family with a probability of oral rehydration solution use corresponding to known levels of oral rehydration therapy access in India.[12]

Costs

The manufacturer (GlaxoSmithKline) recently sold millions of doses to the government of Brazil at a cost of $7 (£4, €4.8) per dose.[13] We used this figure (converted to 2007 rupees) as a baseline estimate for the vaccine's cost and varied it substantially in sensitivity analysis. See bmj.com. We applied an administration cost equivalent to $0.50 a dose. We also varied this value over a wide range, given doubts about the adequacy of many poorer countries' cold chain infrastructure.[14]

We had recent data on direct medical, direct non-medical, and indirect costs from a study of the economic burden of rotavirus treatment in Vellore, India.[11] We weighted the costs reported for each treatment setting (inpatient or outpatient) at each facility by the reported number of encounters in each setting and facility to estimate average costs for inpatient and outpatient treatment.

Cost effectiveness analysis

We determined the incremental cost effectiveness ratio for moving from a strategy of no vaccination to a strategy of universal two dose vaccination with RIX4414. Costs and benefits were discounted at a standard annual rate of 3%. In a secondary analysis, we calculated the incremental cost effectiveness in terms of discounted rupees per disability adjusted life year (DALY) averted (using standard age weighting and discounting). Based on the age specific disability weight for diarrhoea reported in the Global Burden of Disease Study and a typical duration of symptoms of one week, we used a disability weight of 0.0023 per symptomatic episode.

Sensitivity and uncertainty analyses

To assess the overall robustness of our model and to identify influential parameters for which better empirical data are needed, we performed one way sensitivity analyses by individually varying each input parameter. To help us gauge the overall impact of parameter uncertainty, we also performed two dimensional probabilistic sensitivity analysis. See bmj.com.

RESULTS

Base case

The model predicted that, without vaccination, essentially all children would have had a first infection by 60 months of age (consistent with conventional wisdom[3 5 15]), 98.6% would have had a second infection, and 94.4% would have had a third infection. Table 1 shows the projected numbers of clinical events and use of health services per 100 000 children followed for five years under both strategies. Based on an actual Indian birth cohort size of about 25 million a year, each year vaccination would be expected to prevent 1 745 000 severe episodes of gastroenteritis, 1 794 500 outpatient visits, 203 000 admissions to hospital, and 41 000 deaths among children younger than 5 years.

On average, vaccination would be expected to save 0.05390 life years per person, yielding an incremental cost effectiveness ratio of 8023 rupees (or about £100, €113, $164) per life years saved (table 2). The intervention would thus satisfy our cost effectiveness criterion of less than India's per capita gross

Table 1 | Expected clinical events and use of health services related to rotavirus infection in birth cohort of 100 000 Indian infants followed for five years under strategies of no vaccination and vaccination with RIX4414

	No vaccination	Vaccination	Change (%)
Clinical events per 100 000 children			
Any infection	278 672	253 657	−25 015 (−9.0)
Asymptomatic infections	181 164	185 092	3928 (2.2)
Symptomatic infections	97 508	68 565	−28 943 (−29.7)
Severe infections	18 260	11 279	−6981 (−38.2)
Deaths	398	235	−163 (−41.0)
Use of health services per 100 000 children			
Home treatment with oral rehydration solution	73 221	52 191	−21 030 (−28.7)
Outpatient visits	21 582	14 405	−7177 (−33.3)
Admissions to hospital	2367	1555	−812 (−34.3)

Table 2 | Base case cost effectiveness results: strategy of no vaccination compared with strategy of vaccination with two doses of RIX4414

	Mean cost (2007 rupees)	Marginal cost	Mean years of life lost	Life years saved (LYS)	ICER* (rupees/LYS)
No vaccination	106.5	—	2.06627	—	—
Vaccination	538.9	432.4	2.01237	0.05390	8023

*Incremental cost effectiveness ratio (ICER) calculated as marginal cost in 2007 rupees divided by life years saved.

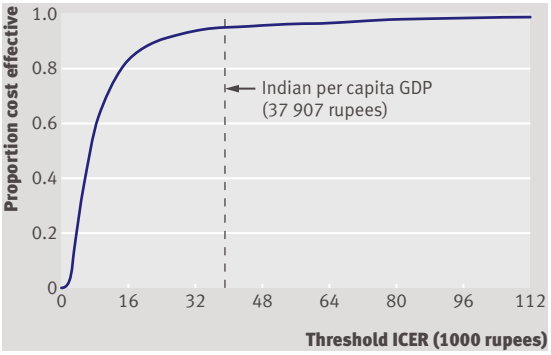

Fig 2 | Acceptability curve for strategy of vaccination with live attenuated human rotavirus vaccine (RIX4414) compared with no rotavirus vaccination. Curve represents probability that vaccination would be cost effective over range of threshold incremental cost effectiveness ratios (ICERs)

domestic product (37 907 rupees in 2007[16]) per life year saved. Taking the broader societal perspective, the incremental cost effectiveness ratio was 7984 rupees per life year saved. With DALYs averted as an alternative measure of effectiveness, the ratio was 6552 rupees per DALY averted

Sensitivity and uncertainty analyses

In a sensitivity analysis, increasing the coverage level for the first and second doses of the vaccine by 10 percentage points increased the reduction in mortality due to vaccination from 41.1% to 47.6%, saving an additional 6500 lives annually population-wide. We also examined the impact of vaccination under a scenario of low efficacy (reduced by 15 percentage points). Even at this level, vaccination could still be expected to save 26 750 lives in one year with an incremental cost effectiveness of 11 647 rupees per life year saved.

We looked at individual parameters which, when varied across their full ranges, most affected the incremental cost effectiveness ratio from baseline. Increasing the probability that children with severe symptoms would present for outpatient treatment by 50% increased the ratio to 51 637 rupees per life year saved, an effect driven mainly by a 92% reduction in mortality that was independent of vaccination status. This was the only individual parameter capable of increasing the incremental cost effectiveness ratio above per capita gross domestic product. See bmj.com.

We explored a scenario in which the overall infection rate, probability of symptoms given infection, and probability that any symptoms would be severe were simultaneously increased by 50%. In this scenario of higher disease burden, absolute mortality reduction per 100 000 due to vaccination rose from 164 to 310 lives, while the incremental cost effectiveness fell to 5007 rupees per life year saved.

Figure 2 shows an acceptability curve summarising the results of our uncertainty analysis. The model was run 1000 times, each time with a different probabilistically sampled parameter set.

DISCUSSION

The results of this study suggest that universal RIX4414 vaccination in India would save many thousands of lives annually across a wide range of scenarios. In the base case analysis, we projected that vaccination would annually prevent 1 745 000 severe episodes of gastroenteritis, 1 794 500 outpatient visits, 203 000 admissions to hospital, and 41 000 deaths among Indian children below the age of 5 at a cost of 8023 rupees (about £100, €113, $165) per life year saved. The projected reduction in mortality was heavily influenced by changes in levels of vaccine coverage, vaccine efficacy, and probability that a severely ill child would receive outpatient care. While incremental cost effectiveness was sensitive to changes in probability of use of outpatient services for those with severe symptoms, parameters influencing disease severity, vaccine cost, case fatality rate, and vaccine efficacy, no scenario in our deterministic sensitivity analysis yielded an incremental cost effectiveness ratio greater than three times the per capita gross domestic product. Only one parameter, when varied to its upper limits, pushed the incremental cost effectiveness ratio above one times the per capita gross domestic product: the probability of outpatient care for the severely symptomatic of 0.863 (versus 0.575 in the base case).

Strengths of study

The model simulates clinical events and use of health services in a temporally explicit fashion that incorporates the changing effects of each individual's age, infection history, and vaccination history on infection risk and response to infection. Vaccine efficacy is adjusted to account for distributions of strains specific to India. Monthly probabilities of infection are based on hazard rates calculated from a meticulously executed birth cohort study, and we used recent cost data.[11]

We found no previously published analyses that examined the impact of rotavirus vaccination specifically in India. One study examined the cost effectiveness of vaccination for low income Asian countries.[17] We consider, though, that these investigators might have substantially overestimated the incidence of admission to hospital, leading to significant overestimation of cost savings from vaccination. Another study was an analysis of rotavirus vaccination in Vietnam.[18] However, rate of rotavirus mortality in Vietnam is substantially lower than that seen in India,[18] and this model did not account fully for changes in the use of health services that would occur as a result of decreased symptom severity.

Net of savings from reduced expenditures on subsidised treatment, we calculated that universal RIX4414 vaccination would cost the Indian Department of Health and Family Welfare 11.6bn rupees (about £140m, €160m, $240m) annually or, for context, about 11.6% of that department's 2006-7 budget. Less expensive rotavirus vaccines might be just a few years away, based on native strains to be manufactured and used in some developing Asian countries, including India.[13 14 19]

Limitations

Incidence and severity parameters in our model were based on results of a Mexican birth cohort study.[6] In sensitivity analysis, we showed that any potential underestimation of disease burden would bias the analysis against the intervention. Less apparent is the direction of any mis-specification of severity dependent probabilities of service use. See bmj.com. In particular, the model's conclusions were sensitive to variation in the probability that those with severe rotavirus disease would receive outpatient care.

Earlier live oral vaccines against rotavirus, as well as those against cholera and polio, have historically performed less well than expected in developing Asian and African countries. This might be because of differences in nutrition and coinfecting pathogens.[7 13 19] Our model does not account for this directly. Finally we did not take into account effects of herd immunity or declines in vaccine efficacy over time because of vaccination induced strain replacement.

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Role of funder: AHRQ played no role in the design or conduct of the study, or in the decision to submit for publication.

Competing interests: None declared.

Ethical approval: Not required.

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How could I have done that?

In mid-1968 I was a preregistration house officer, and the United Kingdom was fearing a flu pandemic. Hong Kong flu (H3N2) had appeared at the start of the year and was ravaging South East Asia. It was predicted to reach UK shores at the end of the year. Matters moved slower then than now.

In September my 2 year old daughter developed a persistent cough. Her GP grandfather was worried about pertussis, so I swabbed her throat for analysis. About a week later, my friend in the microbiology department telephoned. It wasn't whooping cough, but to the microbiology staff's amazement they had grown the Hong Kong flu virus. How on earth had she got it? This was the first appearance of the virus in Europe and was months ahead of schedule. The country was far from prepared, and there was a degree of well controlled consternation in public health circles.

Today, the arrival of Mexican swine flu has got reporters camping outside a Scottish hospital and dominates the news. How things change. In 1968 my daughter's denouement was, to my knowledge, reported, sotto voce, only in the medical press. The stock market did not plummet, we were not besieged by the press, men in body suits and breathing apparatus did not invade my daughter's play group. I just had a couple of chats with a nice woman from Mill Hill who sent me off swabbing the throats of contacts. We never found out how my daughter caught the virus.

In fact, Hong Kong flu did not peak in the UK until the winter of 1970. Worldwide, about one million people died from it.

Later, my friend in microbiology told me that he had heard on the grapevine that a pharmaceutical company was using my daughter's virus to develop a vaccine. He said I ought to write to them as they might wish to express their indebtedness with a small honorarium. "Go on, Phil. What harm can it do?"

Poverty is poverty, and I allowed myself to be persuaded. I still wince at the memory. Was I really that desperate? The company's medical director replied that things must have reached a pretty low ebb for me to resort to flogging my daughter's microbes. He was clearly correct, and moreover the miserable fellow didn't see fit to lift my financial burden, even to the extent of a book token.

As I listen to the news of the impending pandemic, my daughter (a different one) is sniffing in the background and has a sore throat. Let her sniff.

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pico FAST TRACK

Physical interventions to interrupt or reduce the spread of respiratory viruses: systematic review

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STUDY QUESTION How effective are physical interventions in interrupting or reducing the spread of respiratory viruses?

SUMMARY ANSWER Handwashing, personal hygiene, social distancing, and barrier interventions (masks, respirators, gowns, gloves, and goggles) were effective against all forms of acute respiratory tract infections. They work against all viruses and all year round.

Selection criteria for studies

We searched *The Cochrane Library*, Medline, OldMedline, Embase, and CINAHL, without restrictions on language or publication type, for any intervention to prevent viral transmission of respiratory viruses (isolation, quarantine, social distancing, barriers, personal protection, and hygiene). We included randomised trials and cohort, case-control, crossover, before and after, and time series studies that compared physical interventions with each other or with standard practice.

Primary outcome(s)

Outcomes studied were numbers of cases of acute respiratory tract infections, transmission rates, and harms associated with physical interventions.

Main results and role of chance

Hygiene measures and barriers were effective against severe acute respiratory syndrome: handwashing more than 10 times daily (odds ratio 0.45, 95% confidence interval 0.36 to 0.57; number needed to treat=4, 95% confidence interval 3.65 to 5.52), wearing masks (0.32, 0.25 to 0.40; NNT=6, 4.54 to 8.03), wearing N95 masks (0.09, 0.03 to 0.30; NNT=3, 2.37 to 4.06), wearing gloves (0.43, 0.29 to 0.65; NNT=5, 4.15 to 15.41), wearing gowns (0.23, 0.14 to 0.37; NNT=5, 3.37 to 7.12), and handwashing, masks, gloves, and gowns combined (0.09, 0.02 to 0.35; NNT=3, 2.66 to 4.97). Combined use of handwashing and masks reduced household transmission of influenza if used within 36 hours of development of symptoms in the index case (adjusted odds ratio 0.33, 95% confidence interval 0.13 to 0.87). The spread of respiratory viruses can be prevented by hygiene measures in younger children. Additional benefits from reduced transmission from children to other members of the household, by gargling, extensive mask wearing, and social distancing are only broadly supported from studies with the greatest potential for confounding. The effectiveness of masks is affected by low compliance due to discomfort and rashes.

Bias, confounding, and other reasons for caution

Study quality was variable and some interventions such as gargling, addition of antiseptic to handwashing, exposure based triage and social distancing, and obstacles to the introduction of school based handwashing programmes need further evaluation.

Study funding/potential competing interests

This study was supported by the NHS research and development programme and National Health and Medical Research Council of Australia. We have no competing interests.

MAIN FINDINGS OF SYSTEMATIC REVIEW OF PHYSICAL INTERVENTIONS TO REDUCE THE SPREAD OF RESPIRATORY VIRUSES

Physical intervention	Intervention effective	Interpretation
Handwashing	Yes	Physically removes virus
Barriers (masks, gloves, gowns, goggles)	Yes	Prevents contact or inhalation of virus
Social distancing	Probably	Alters environmental conditions for transmission
Gargling	Probably	Dilutes or neutralises virus (observation is based on a single study)
Adding antiseptics to barriers and hygiene measures	Unknown	May dilute or neutralise virus
Combined interventions	Yes	Removes virus and alters environmental conditions for transmission

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Prostate specific antigen for early detection of prostate cancer: longitudinal study

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STUDY QUESTION Does prostate specific antigen test attain validity standards required for screening?

SUMMARY ANSWER No cut-off value for prostate specific antigen attained likelihood ratios formally required for a screening test, although prostate specific antigen concentrations below 1.0 ng/ml virtually ruled out a diagnosis of prostate cancer during follow-up.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS The performance of prostate specific antigen testing for early detection of prostate cancer is good overall. These data, in combination with data from recent screening trials, indicate that further biomarkers are needed before population based screening for prostate cancer should be introduced

Participants and setting

We identified 540 incident cases of prostate cancer and 1034 controls matched for age and date of blood draw within the longitudinal Västerbotten Intervention Project cohort, Umeå, Sweden.

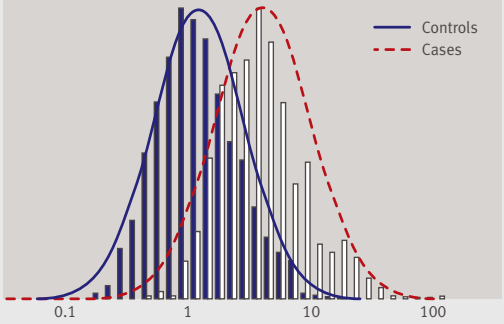
Design, size, and duration

This nested case-control study used record linkage of the cohort to the regional cancer registry. Concentrations of prostate specific antigen were measured in cryopreserved plasma drawn at a mean time of 7.1 years before diagnosis from cases and controls. Clinical characteristics of the tumours, including local stage, lymph node stage, metastases at bone scan, tumour differentiation, and serum prostate specific antigen concentrations at the time of diagnosis, came from the Northern Sweden part of the National Prostate Cancer Register of Sweden.

Main results

The median plasma concentration of prostate specific antigen was 3.6 ng/ml among cases and 1.1 ng/ml in controls. In the full group, the area under the curve for prostate specific antigen was 0.84. It was higher for cases with a short lag time than for those with a long lag time, higher among cases aged under 59 at the time of recruitment than in those over 59, and higher for high risk tumours than for low risk tumours. At prostate specific antigen cut-off values of 3, 4, and 5 ng/ml, sensitivity estimates were 59%, 44%, and 33%, and specificity estimates were 87%, 92%, and 95%. The difficulties in finding a prostate specific antigen cut-off value resulting in a sufficiently high specificity concurrently with a reasonably high sensitivity (that is, above 50%) are graphically illustrated in the figure by the large overlap in the distribution of prostate specific antigen concentrations in cases and controls. The positive likelihood ratio commonly considered to "rule in disease" is 10; in this study, the positive likelihood ratios were 4.5, 5.5, and 6.4 for prostate specific antigen cut-off values of 3, 4, and 5 ng/ml. The negative likelihood ratio commonly considered to "rule out disease" is 0.1; in this study, the negative likelihood ratios were 0.47, 0.61, and 0.70 for prostate specific antigen cut-off values of 3, 4, and 5 ng/ml. The negative likelihood ratio for a prostate specific antigen cut-off of 1.0 ng/ml was 0.08. Six (1.2%) cases with prostate specific antigen concentrations below 1.0 ng/ml were diagnosed as having high risk prostate cancer, and for those men the time between blood draw and diagnosis was between five and 13 years.

DISTRIBUTION OF PLASMA PROSTATE SPECIFIC ANTIGEN (PSA) CONCENTRATIONS IN CASES AND CONTROLS



Curves indicate frequency functions of calculated normal distribution of logarithm of PSA concentrations according to mean and SD in cases and controls. Histogram shows observed distribution of logarithm of PSA concentrations in cases and controls

Bias, confounding, and other reasons for caution

The lack of long follow-up is a limitation of our study.

Generalisability to other populations

The results of this study can be extrapolated to other white European populations in which no widespread screening with prostate specific antigen tests is ongoing.

Study funding/potential competing interests

This study was supported by grants from the Swedish Cancer Foundation and the Lion's Cancer Research Foundation at Umeå University.

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Economic evaluation of arthritis self management in primary care

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STUDY QUESTION Is an arthritis self management programme in addition to an education booklet and usual care cost effective compared with an education booklet and usual care alone?

SUMMARY ANSWER No, the programme was not cost effective on the basis of current cost perspectives and quality adjusted life year (QALY) thresholds from the National Institute for Health and Clinical Excellence. The probability of cost effectiveness was greater when broader costs and other quality of life outcomes were considered.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Evaluations of arthritis self management programmes in the United States have suggested that they can provide patient centred benefits and reductions in healthcare use, but the applicability of this evidence to the UK was unclear. Our study does not suggest cost effectiveness on the basis of current policy perspectives but it does suggest a greater chance of cost effectiveness if broader cost and outcome perspectives are taken.

Main results

At 12 months, mean health and social care costs (at 2002-3 prices) were £101 higher (95% confidence interval £3 to £176) in the self management group. There were no significant differences in societal costs, which were up to 13 times the size of health and social care costs. From the health and social care perspective the intervention was dominated by the control based on QALYs and had incremental cost effectiveness ratios between £279 and £13 473 for other outcomes. From the societal perspective the self management programme seemed superior to the control owing to (non-significant) lower costs and (non-significant) better outcomes on all measures except QALYs. Probabilities of the programme's cost effectiveness were low based on QALYs and ranged between 12% and 97% (for thresholds ranging from £0 to £1000) for one point improvements in SF-36 outcomes, but the clinical significance of this is debatable.

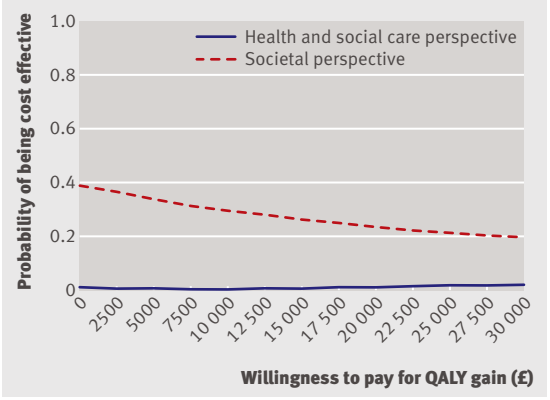
Design

This was a cost effectiveness and cost utility analysis alongside a randomised controlled trial from health and social care and societal perspectives (ISRCTN 79115352).

Source(s) of effectiveness

Overall, 812 participants aged ≥50 years with osteoarthritis of the hips or knees, or both, and pain or disability, or both, were recruited from 74 general practices in the UK. They were randomised to receive usual care plus either six sessions of an arthritis self management programme and an education booklet or the booklet alone. All cost and outcome assessments were carried out at baseline and at four and 12 months.

PROBABILITY OF ARTHRITIS SELF MANAGEMENT PROGRAMME PLUS EDUCATION BOOKLET BEING COST EFFECTIVE



The primary outcomes were the physical and mental health component summary scores of the SF-36. The EuroQol was used to estimate QALYs. At 12 months there were no significant differences in these outcomes.

Data sources

Individual level data on resource use related to arthritis were collected using an adapted client service receipt inventory, administered as a self complete questionnaire referring to the previous three months. The unit cost for the self management programme was estimated as an average cost per person based on rates paid by the trial to Arthritis Care for running the courses. National unit costs were applied to other resource use to estimate total three month costs at 12 months (at 2002-3 prices).

Results of sensitivity analysis

We explored the impact of data being missing on resource use or cost using imputed full sample data to compute alternative incremental cost effective ratios; this did not alter broad conclusions. Increasing the unit costs of the self management programme did not alter any cost related conclusions, but reducing the unit cost by between 20% and 50% led to total health and social care costs no longer being significantly different between the groups.

Limitations

Our unit cost for the self management programme didn't include additional resources associated with course development, failed courses, or coordination, but an assumption of higher costs would not alter conclusions about total costs.

Study funding/potential competing interests

This study was funded by the UK Medical Research Council. We have no competing interests.

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Filtering Medline for a clinical discipline: diagnostic test assessment framework

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STUDY QUESTION Can clinicians filter Medline to search for articles within a clinical discipline, rather than searching the entire database?

SUMMARY ANSWER Medline can be filtered for nephrology in a reliable manner, and filters could be developed for other clinical disciplines by similar methods.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Previous attempts to filter Medline for a clinical discipline have met with limited success. This study shows Medline can be filtered for a clinical discipline in a reliable manner, with the best renal filters having a sensitivity and specificity in excess of 97%.

Participants and setting

We aimed to develop high performance filters for a clinical discipline in medicine. We chose renal medicine as clinical information for this discipline is published across hundreds of multidisciplinary journals and is difficult to track down.

Design, size, and duration

We used a diagnostic test assessment framework with a development and validation phase. Each article from a sample of 4657 articles published in the year 2006 from 40 journals was manually reviewed, and 19.8% contained information relevant to the discipline of nephrology. We compared the performance of 1 155 087 unique renal filters with that of the manual review.

Main results and the role of chance

We calculated the sensitivity, specificity, precision, and accuracy of each filter. The best renal filters combined 2-14 terms or phrases, and included the terms "kidney" with multiple endings (that is, truncation), "renal replacement therapy", "renal dialysis", "kidney function tests", "renal", "nephr" truncated, "glomerul" truncated and "proteinuria". These filters achieved peak sensitivities of 97.8% (95% CI 96.6% to 99.0%) when keeping specificity >90%, and peak specificities of 98.5% (98.0% to 99.0%) when keeping sensitivity >90%. Filter performance remained excellent in the validation phase.

To examine the filters' usefulness, we asked five clinicians independent of the research team to conduct a PubMed search for a single focused clinical question. Each clinician was asked to search for articles on one of five topics: renal effects of statins, the benefits of fenoldopam in acute kidney injury, the benefits of tacrolimus compared with cyclosporin in kidney transplantation, the efficacy of low dose dopamine in acute kidney injury, and the benefits of intradermal versus intramuscular hepatitis B vaccination in chronic kidney disease. Clinicians retrieved more clinically relevant articles when they used these filters (see example below).

Bias, confounding, and other reasons for caution

These filters help only with the renal components of any search. Limitations of the accompanying terms will influence performance of searches. Some articles are never indexed in Medline or may never be retrieved because of poor indexing.

Generalisability to other populations

To improve searching, Medline can be filtered for a clinical discipline. By filtering the database to perform the search within a discipline of interest, the likelihood of retrieving relevant information with the remaining search terms is increased.

Study funding/potential competing interests

This study was funded by the Kidney Foundation of Canada. AXG was supported by a Clinician Scientist Award from the Canadian Institutes of Health Research. The researchers were independent of the funders, who had no role in the design, execution, or reporting of the study. No competing interests declared.

RESULTS OF A MEDLINE SEARCH WITH AND WITHOUT SEARCH FILTERS

Clinical question	No of relevant articles retrieved			No of non-relevant articles retrieved for each relevant article		
	Without filters	With best sensitive filter	With best specific filter	Without filters	With best sensitive filter	With best specific filter
When tacrolimus is compared directly with cyclosporin in the treatment of kidney transplant recipients, what is the evidence on transplant outcomes, toxicity and adverse effects? (63 relevant articles)	10	60	60	18	20	15

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