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Economic analysis on *Haemophilus influenzae* b, chickenpox, pneumococcal, hepatitis A and combination vaccines in the Childhood Immunisation Programme in Hong Kong

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Key messages

1. Cost-effectiveness models using local data on incidence and costs were constructed for 4 childhood vaccines: pneumococcal, varicella, *Haemophilus influenzae* b (Hib) and hepatitis A (hep A).
2. Pneumococcal vaccine appears highly cost-effective at a cost of $50,000 per life year saved in the main model tested and has a benefit:cost ratio of 1.7:1.
3. Hib vaccine, at a cost of $160,000 per life year saved, still falls within accepted thresholds of cost-effectiveness when given as a monovalent vaccine although, with a very conservative estimate of value of a life year, the benefit:cost ratio is only 0.8:1.
4. The varicella and hep A models had more uncertainties and further modelling might be indicated for these vaccines perhaps in conjunction with adult vaccines.
5. The models show the burdens of these 4 diseases and can be further developed and adapted as new assumptions and data become available in future.

Introduction

The intent of this study was to provide information to enable the Scientific Committee on Vaccine Preventable Disease (SCVPD) to recommend changes to the infant vaccination programme. The study aims were revised to exclude polio and acellular pertussis and add a simple model of hep A vaccine.

Aims and Objectives

The aim of the study was to provide cost-effectiveness information on childhood vaccines in the setting of Hong Kong to assist the SCVPD in coming up with recommendations on vaccines to be used in future childhood immunisation programmes.

The revised principal questions were:

1. whether to introduce varicella vaccine in infants
2. whether to introduce Hib vaccine in infants
3. whether to introduce pneumococcal vaccine in infants
4. what combination vaccines are available for use in Hong Kong and what is their likely cost-effectiveness? (only the Hib combination vaccine was finally considered)
5. whether to introduce hep A vaccine in infants

Methods

Each vaccine model necessarily differed according to the type of model most suitable, the epidemiology of the condition and the data available. For the details of each model and costing procedures, the reader is referred to the main report but a summary is given below:

For each economic model:

- A decision-tree of the disease with and without vaccination was constructed using local data on incidence and overseas data on vaccine efficacy.
- Hypothetical birth cohorts of all infants born in Hong Kong were constructed and their health states followed over the appropriate number of years both with vaccination and without vaccination.
    - For the pneumococcal, Hib and hep A vaccines we used a simple Markov model based on a cohort simulation to follow the health states of a single year's cohort of births for 5 years for Hib (since children over 5 at are low risk) and until death for pneumococcal and hep A vaccines. The pneumococcal model included the impact of herd immunity on adults and all three estimated cases of disease, health care utilisation and costs and lives lost or saved over one year after vaccination.
    - For varicella, a realistic age-structured transmission dynamic model originally developed in Canada was adapted to the Hong Kong population parameters; this model estimated cases of both varicella and zoster in children and adults

over 80 years after vaccination. A separate costing model was created to estimate the utilisation, monetary costs and impact on life years of the numbers of cases calculated in the dynamic model and an estimate for one year was calculated by dividing the total by 80.

- Differences in the rates of diseases with and without vaccine, plus sequelae, associated savings and life years saved between the two cohorts of infants were taken as benefits of vaccination.
- Direct and indirect costs were included.
- Cost-effectiveness analysis was conducted from both the societal (includes everyone's costs) and the public health care provider's (government) perspectives.
- A main model was constructed in each case which used conservative estimates but was also based as far as possible on realistic data. Sensitivity analyses of assumptions and estimates were done and the results of the most important estimates or those which most affected the results are given in the individual chapters.
- Saved life years were used as the main benefit measure in the cost-effectiveness ratios and costs were estimated as net costs which were calculated by subtracting the monetary value of the savings in utilisation from the programme costs using both the societal (includes everyone's costs) and government's perspectives. The primary outcome of each model was the net cost per life year saved. Benefit:cost ratios were also calculated by valuing the life years saved using a human capital approach where each life is only valued as the number of potential productive years times average salary, summing the total monetised benefits and dividing by the total costs. This produces a very conservative estimate of the benefit:cost ratios.
- Costs included the price of the vaccine and costs of administering and storing it. Benefits included avoided public and private hospitalisations, accident and emergency visits, public and private outpatient visits, sequelae costs, child and parent travel costs due to hospitalisations and doctor visits and productivity losses of parent due to hospitalisations and outpatient visits.
- Since the vaccines were to be compared with one another, we used cost per life year saved as a common measure of outcome. Using cost per quality-adjusted life year (QALY) would have required further comparable information on the utilities of relevant conditions.

Assumptions, results and discussion

The following sections on assumptions, results and discussion are presented by vaccine for ease of understanding.

Pneumococcal vaccine

Main assumptions

- coverage rate after implementation was 100% and current coverage was zero.
- the transition probabilities between health states in the cohort model were independent of the states and of history of infection.
- the incidence rates of pneumococcal meningitis and pneumococcal septicemia were the same as the Hospital Authority (HA) hospital discharge rates boosted by a factor of 3.5 to compensate for under-reporting.
- vaccine efficacy against invasive disease was 89.1%, all-cause pneumonia 6% and acute otitis media 6.4% (Black et al., 2000).
- protection by vaccine only started after all injections had been received; both four and three-dose schedules were modelled.
- vaccine protection decreased by 1% and 3% per year for ages 0 to 5 and 6 to 10 respectively and there was no protection after 10 years.
- the cost of the vaccine was $500 per dose and storage was an extra 10%.
- there were no extra staff, advertising or other administration costs, no vaccine wastage and no side effects of vaccination.
- hospital admissions from both the private and public (HA) sectors were included but sequelae treatments costs were all in the public sector.
- the unit costs per hospital bed-day for children were the same as those for adults which equalled the charges to non-eligible persons for a bed-day in a public hospital.
- all admitted meningitis and septicaemia cases had two general practitioner visits either private or public.
- there was one extra non-hospitalised pneumonia case for every hospitalised case.
- each hospitalised and community pneumonia case had three doctor visits.
- each hospital and community case of acute otitis media had two doctor visits but there were no deaths.
- all treatment and procedure costs were included in the unit costs of public and private bed-days and outpatient visits.
- there were no over-the-counter medication or self-care costs.
- only meningitis cases had sequelae with similar types and proportions of hearing loss as in the UK study; all sequelae occurred at age 2.
- disabled individuals from age 2 to 64 would apply for Social Security Allowance (SSA).

- each case of deafness had one audiology and one audiometry test each year until age 64.
- avoided travel costs for the sick child and accompanying person assumed a roundtrip of 5 kilometres by taxi.
- there were no indirect costs of vaccination for the four dose schedule but, for the three-dose schedule, one parent took a half day off work for each dose at the median hourly salary in 2005 plus travel costs.
- the vaccination of one infant cohort reduced the incidence of pneumococcal pneumonia (Model 1) or all-cause pneumonia (Models 2 and 3) in unvaccinated persons aged 20 and over for one year (herd immunity effect) but Model 4 assumed no herd immunity.
- for Model 1, reduction in pneumococcal pneumonia was assumed to be the same as the observed reduction in invasive pneuomococcal disease (IPD) found in US by Whitney et al. (2003).
- Model 2 used the significant results observed in a US time-series analysis (Grijalva et al., 2007) for the reduction in all-cause pneumonia; Model 3 used the observed results whether significant or not.
- no adjustment was made for different prevalent serotypes from those in US.
- no effects of serotype replacement were included.
- utility values from UK were used for calculating QALYs.

Results

Under the above assumptions made, the implementation of universal pneumococcal vaccination of infants was cost-effective at just over $50,000 per life year saved from a societal perspective. The cost per life year saved was only slightly higher ($59,000) from the government perspective. The cost per QALY gained was $51,312 and $55,987 from societal and government perspectives respectively. The biggest impact on the results is from the assumption made regarding the herd immunity effect. The Main model assumes an impact only on invasive disease but that this impact extends to adults. If it was assumed that herd immunity also applies to all cause pneumonia, then the vaccine could be cost-saving. The cost-effectiveness acceptability curve shows that the probability that vaccination is cost-effective is over 50% for any value of a life year over about $40,000 which is a low value by international standards. The benefit:cost ratio is 1.7:1 for the scenario which confers herd immunity against pneumococcal pneumonia only.

Discussion

The main uncertainty was the impact of herd immunity on all cause pneumonia and we therefore modelled a variety of alternative scenarios. However, even assuming that the impact is only on IPD in adults, the vaccine still appears to be cost-effective at a cost of around $50,000 per life year saved which would be considered a cost-effective intervention

according to any existing guidelines. The majority of the saved life years are in older people i.e. 100 of 108 saved lives are adults. Pneumococcal vaccine is currently relatively expensive at around $500 per dose giving an annual cost of $126 million to vaccinate one cohort but with an estimated 1,500 life years saved from avoided IPD. Whether serotype replacement would occur, reducing the efficacy of the vaccine after a vaccination programme is implemented was not modelled in this analysis but is a possibility according to US evidence and should be monitored.

Chickenpox vaccine

Main assumptions

- the force of infection, duration of latent and infectious periods and proportion of contacts that boost against zoster were as in the UK model.
- incidence rates were estimated by the model using a stable population modelled on Hong Kong demographics.
- the coverage of the vaccine after programme implementation was 90% every year but the current coverage rate was zero.
- vaccine efficacy was 93% as in the UK model (Brisson et al., 2000).
- protection only started after all injections had been received.
- there were no extra costs of clinic attendance for vaccination, nor staff, advertising, invitation or vaccine wastage costs or side effects.
- breakthrough cases had a five-fold lower risk of hospitalisation than natural cases but length of stay (LOS) in hospital was the same.
- the costs per hospital bed day for children were the same as for adults and equalled the charge to non-eligible persons for a bed-day in a public ward.
- infection control measures cost HK$10,000 per hospitalised case.
- the proportion who visit a doctor for chickenpox or zoster in a child equals that for a case of mild or serious illness respectively as obtained in the Children's Telephone Survey.
- all those 65 or over with chickenpox would visit a doctor and the intermediate age groups of 15-44 and 45-64 were extrapolated.
- all adult breakthrough cases had one doctor visit, those with natural chickenpox up to two and those with zoster up to three.
- all procedure and treatment costs were included in the unit costs of visits.
- there was no over-the-counter medication and self-care costs.
- there were no sequelae costs.
- travel costs for the sick child and accompanying person was a roundtrip of 5 km by taxi.
- lost working time of a hospitalised case (or one parent if the case is a child) amounted to the hospitalisation period plus two days.

- lost working time for a clinic visit and sick leave amounted to eight days for a case or one parent of 8.3% of child cases as estimated from the survey.
- vaccination of infant cohorts reduced the incidence of infection in vaccinated and unvaccinated persons (herd immunity) of all ages.
- breakthrough cases did not result in deaths.

Results

Over the 80 years following its initiation, vaccination of infants would not be cost beneficial in that the costs would be greater than the benefits principally because of the costs of increased zoster cases. The greatest uncertainty in this analysis is whether reduced exposure to circulating wild-type virus will cause an increase in zoster cases in older people. This might be answered in the coming years from the experience in US. The extra zoster cases after vaccination which are predicted by the model would decline after 50 to 80 years since vaccinated children will probably be less susceptible to zoster when they are older. Therefore in the very long term, infant vaccination could become cost-beneficial.

Discussion

For varicella vaccine, the impact of a childhood vaccine programme is less certain than for pneumococcal vaccine because of the current lack of evidence on whether reduced exposure to varicella would increase the incidence of zoster (shingles) in older people with its consequent morbidity and mortality. The model rests on assumptions about the combined epidemiology of these two conditions and there is no firm evidence to date on whether these assumptions are correct. Assuming that they are correct, then the vaccine is not likely to be cost-effective. With a value of life based only on lost production and favourable efficacy estimates, the vaccine could be cost-effective. One option for this vaccine is to delay a decision until more definite information is obtained on the impact on zoster in US where infant vaccination has already been implemented. Another is to consider an adolescent vaccine which appears to be the most cost-effective option in other countries when the effect on zoster is taken into account. Finally a vaccine against zoster in older people could be considered. Combined with an infant vaccination programme, this might remove the unfavourable negative effects of infant vaccination on zoster. Neither of the two non-infant vaccines were included in this model.

Hib single vaccine and combination vaccine

Main assumptions

- in the cohort model, transition probabilities between health states were independent.
- all invasive Hi diseases as reported in the HA discharge data were caused by Hib.

- current coverage rate of zero for vaccination.
- protection by vaccine only started after all injections had been received.
- there was no lost working time of parents due to attendance for vaccination.
- the efficacy of the vaccine against invasive Hib disease (84%) lasted up to age 5.
- efficacy of the combination vaccine was the same as the monovalent vaccine.
- the price of the combination vaccine was $250 and there was no extra storage cost.
- the monovalent vaccine had a wastage rate of 10%, the combination vaccine of zero.
- there were no side effects.
- the age-specific incidence rates of Hib meningitis and septicaemia for under 5s were the same as hospital discharge rates.
- all serious sequelae were treated in public hospitals.
- the cost per hospital bed-day for a child was the same as for an adult and equalled the charge to non-eligible persons for a bed-day in a public ward.
- all Hib meningitis and septicaemia cases had two doctor visits prior to admission.
- there was one extra community bacteraemic pneumonia case for every hospitalised case.
- each bacteraemic pneumonia case had three prior doctor visits.
- each public hospital case had one emergency department visit.
- all procedure and treatment costs were included in unit costs of doctor visits.
- there was no over-the-counter medication or self-care.
- only meningitis cases resulted in sequelae; types of sequelae and proportions of cases was the same as in the US study.
- disabled individuals aged 2 to 64 would apply for SSA.
- each disabled child aged 2 to 11 would have assessments and rehabilitation; those who became deaf would have an audiology consultation and hearing test each year until age 64.
- travel costs for the sick child and accompanying person was a roundtrip of 5 km by taxi.
- there were no herd immunity effects.

Results

For Hib vaccine, the model predicted that two deaths would be avoided in one birth cohort of children giving a cost per life year saved of $160,000 in the Main model. The cost of the combination vaccine which includes Hib appears to be much higher in Hong Kong than the combination vaccine which does not and thus it did not appear to be cost-effective. The benefit to cost ratio was 0.8:1. This was a relatively conservative model which did not take any herd immunity effect on non-vaccinated children into account but it is not clear that this would have made a large impact. It was also conservative in the valuation of life years resulting in a low benefit:cost ratio.

Discussion

For Hib vaccine, a cost-effective result was obtained using the Main model if a life year is valued at $160,000 or more. This programme would only cost $12 million to vaccinate an annual cohort of children using the monovalent vaccine. The combination vaccine costs so much more that it appears not to be cost-effective at present. The main uncertainties in this model are the current incidence of Hib (we assumed about 2 cases per 100,000 children under 5) and the possible impact on herd immunity. If we have overestimated the incidence of Hib, then the real cost-effectiveness could be lower. If there is an impact on disease in unvaccinated children or adults then the true cost-effectiveness might be higher. We have used cost per life year rather than cost per QALY as the outcome, which ignores the potential benefit of vaccination to avoid reduction in quality of life of those children who suffer a serious complication and are left with long term disability. We have designated these as government costs which means that the societal and government perspectives in this model are not very different. We have underestimated the savings in costs to families and communities from avoiding the impacts of Hib disease. We have not included any benefits of avoiding milder i.e. non-invasive Hib illness due to vaccine. Thus the cost-effectiveness of Hib vaccine could be under-estimated. In the calculation of benefit:cost ratio, the valuation of a life year, using the human capital approach, as only the production loss avoided clearly underestimates the value of the benefits.

Hepatitis A vaccine

Main assumptions

- the coverage rate was 100%.
- the age-specific notification rates would decline at an annual rate of 2.1% for all ages reaching a 53%, 73% and 84% decline by the time the 2005 birth cohort reached ages 25, 50 and 75 years, respectively.
- the rate of reporting cases was 50% giving one unreported case for each reported one.
- the efficacy of hep A vaccine was 99% (Jacobs et al., 2003); 50% would lose protection within 30 years at a linear rate of 2.3% per year.
- protection by vaccine only started after all injections had been received.
- asymptomatic cases would not incur any costs.
- there were no staff, advertising, letter, phone call costs, vaccine wastage or side effects.
- costs per bed day for children were the same as for adults and equalled the charges to non-eligible persons for a bed-day in a public ward.
- the rate of liver transplant was the same as in the US.
- the cost of a liver transplant was $185,150 (an ultra-major III operation in public hospital).

- notified cases had 3 outpatient visits symptomatic but not notified had 2 and public hospital cases had one emergency clinic visit.
- all procedure and treatment costs were included in the unit costs of visits.
- there were no over-the-counter medication, self-care or sequelae costs.
- travel costs for the sick child and accompanying person were a roundtrip of 5 km by taxi.
- hospital cases would have 20 or 60 days sick leave after the hospital stay for mild and severe cases respectively.
- two work days were lost for doctor visits for every adult case and parent of a child case.
- there were no benefits from herd immunity.
- the age-specific case-fatality rates were the same as in the US.

Results

For hep A vaccine, the simple model developed showed a very high cost per life year saved but did not include herd immunity effects or impact on quality of life which, in this case, could have been quite large.

Discussion

The model constructed for hep A vaccine is a very simple model and does not demonstrate cost-effectiveness of the vaccine since it only included impact on disease in the vaccinated children and such disease in children is usually mild and often self-limiting. Also, we only modelled the impacts on monetary costs of illness and loss of life but a large cost is potential loss of quality of life when ill. The largest impact of the vaccine could be in reducing disease in older people who tend to have more severe disease. To estimate this we would require a more detailed model which was beyond our resources in this study. This might be considered and, in this case, it would be useful to include a model of an adolescent/adult vaccine with or without prior screening of susceptibility as a comparison. Given the high cost per life year obtained from this model, it is likely that the vaccination will only appear cost-effective if there is a large herd immunity effect and if quality of life is included as an outcome.

Overall comments and conclusion

As far as possible, all vaccines were modelled in a similar way in order to provide comparable information. All costs, except for a few such as infection control costs, were based on local data and local admission to hospital, deaths and notifications were used to estimated incidence, admission rates and case-fatality rates. As far as possible, local data on complications were used but, in some cases, these were taken from overseas literature or models and validated locally. Vaccine efficacy data was taken from overseas literature and the most up to date evidence was used. There were a number of uncertainties and limitations in the models and these were subjected to sensitivity analyses. Details are given in each

chapter in the main report. We assumed a high coverage for each vaccine because the current childhood programme has high coverage and most vaccines modelled would fit into the current schedule.

This study was carried out to provide information on which the SCVPD could base decisions about the introduction of new vaccines in the Childhood Immunisation Programme. The results for pneumococcal and Hib vaccines show cost-effectiveness at $50,000 per life year saved and an annual cost of $126 million for pneumococcal vaccine and $160,000 per life year saved and annual cost of $12 million for Hib vaccine. Varicella and hep A vaccines had more uncertainties and further modelling might be indicated for these vaccines perhaps in conjunction with adult vaccines. The models, which are mostly in Excel spreadsheets, show the burdens of these 4 diseases based on local data and can be further developed and adapted as new assumptions and data become available in future.

Policy implications

The recommendation from this report would be to include pneumococcal vaccine in the Childhood Immunisation Programme since it is clearly cost-effective as modelled. The Hib vaccine should also be considered for inclusion given that even using a very conservative model, the cost per life year falls below normally accepted thresholds of value. A decision on varicella vaccine could be deferred until the question of its impact on zoster (shingles) is resolved or the impact of an adolescent varicella or elderly zoster vaccine could be modelled. With the freed resources, a simple model of hep A vaccine was developed. This model with some further development to include herd immunity and quality of life effects, can be used as the basis of a comparison of future options regarding hep A vaccination e.g. an adolescent or adult vaccine programme.

This study provides new knowledge about the cost-effectiveness of additions to the childhood vaccines in the setting of Hong Kong. The findings will assist the Scientific Committee on Vaccine Preventable Diseases under the Centre for Health Protection to recommend vaccines to be used in future childhood immunisation programmes in Hong Kong. This study also provides information on burden of infectious disease which will be of use in future research. The models can be amended in future to reflect new data or assumptions.

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