



Economics of Rotavirus Gastroenteritis and Vaccination in Europe: What Makes Sense?

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Abstract

Rotavirus is a major cause of gastroenteritis in children throughout Europe and the world. In addition to causing morbidity and mortality in children, rotavirus gastroenteritis (RVGE) creates a major economic burden on health care systems and families in Europe. The costs of hospital admissions for RVGE and nosocomial infections generate significant medical treatment costs throughout the region. Less information is available on the costs associated with less severe episodes and the costs borne by families, including lost time from work. The availability of rotavirus vaccines presents an effective opportunity to prevent RVGE and these associated economic costs, as well as providing protection to each child and hence benefiting the child's family. The adoption of rotavirus vaccine by health authorities in Europe will require a comparison of the costs and benefits. Economic evaluations that compare the costs of vaccination to the economic benefits of rotavirus vaccination will provide an estimate of its financial impact on health care systems and society. However, to provide a complete picture, economic evaluations of rotavirus vaccines will need to account for both the reduced costs and the reduced morbidity from prevented RVGE. Cost-effectiveness analyses based on quality-adjusted life years (QALYs) provide a systematic approach for assessing vaccination as a health investment, comparing the incremental costs associated with rotavirus vaccination and the reduced morbidity and mortality. QALYs provide a standardized approach for quantifying and comparing reductions in health-related quality of life and premature mortality. Although methodologic limitations exist in applying the QALY approach to childhood vaccines, their use in cost effectiveness analyses allows decision makers to consider the full health benefits of rotavirus and other vaccines.

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Rotavirus (RV) infection is the single most important cause of diarrheal illness in small children in developed and developing countries. Gastrointestinal infections in children have a wide range of impacts on their families and society, including increased medical expenditures, lost productivity, other costs to households for the care of children, and pain and suffering caused to children and their families.

As effective rotavirus vaccines become available, policy makers will have to make decisions regarding the relative costs and benefits of vaccination in addition to considering its clinical effectiveness. In doing so, they must systematically consider the economic burden of disease, the impact of vaccination on health and economic outcomes and the net costs of vaccination and compare the costs of vaccination to the health benefits.

The purpose of this article is to review the existing data on the economics of rotavirus gastroenteritis (RVGE) in Europe and suggest the types of economic evaluations that will be useful in assessing the merits of vaccination. In particular, it will address how economic evaluation can be used to assess the value of vaccination as a health investment through cost effectiveness analyses using health improvement measures such as quality-adjusted life years (QALYs).

ECONOMIC IMPACT OF RVGE IN EUROPE

Types of Costs. RVGE generates a variety of costs for the health care system (direct medical costs), families of those infected (nonmedical direct costs) and society as a whole (indirect costs). Medical costs relate to the costs of office visits, emergency room visits and inpatient stays. The costs include laboratory, professional services, medication and other treatments. In Europe, because the existence of National Health Services, few of these costs are borne by affected families; more typically, they create a burden for the health care system of the country.

Nonmedical direct expenses include the out-of-pocket expenses paid by households that are not related to medical care, including additional liquids, additional diapers, additional costs of child care and the costs of traveling to receive medical care. These costs are borne primarily by the families of children with RVGE.

Besides the emotional impact of disease on children and their families, moderate to severe episodes of RV diarrhea also result in significant societal and household costs because of lost work time, often referred to as indirect costs. These costs are incurred as parents are forced to stay home

from work to care for sick children. This lost time from work results in a societal cost, because of the reduction in labor productivity. It can also result in an economic impact on individual households if parents are self-employed or otherwise lose wages as a result of their absence. In addition to the lost time from paid employment, RVGE can also result in time lost from other productive activities (such as household work) and leisure activities. These activities also have an economic value to society and can be included in estimates of indirect costs, but their economic value is difficult to measure. *Costs of RVGE Hospitalization.* Empirical estimates are available for some of these costs resulting from RV hospitalizations and outpatient visits in different European countries. Studies of medical costs of hospital admissions for RVGE have been published for Austria,¹ Scotland,² Spain,³ Ireland,⁴ Sweden⁵ and England^{6,7} (Table 1). The study by Fruhwirth et al¹ estimates the cost of community-acquired cases resulting in medical visits for RVGE (hospital or

office). Studies of the burden of outpatient visits and hospital admissions for RVGE are based on estimates of incidence and mean cost per case. Most of the studies above focus on the direct medical costs associated with treatment and thus use health care system perspective (or centralized provider such as a national health system).

The studies differ in their approaches. Some^{2,3,5} use national surveillance data on the incidence of RV hospitalizations combined with standard medical cost estimates (based on bed-day costs or reimbursement rates) to estimate national economic burden. Others^{1,6,7} use detailed cost data for specific communities or facilities to estimate a cost per case. The former method provides more representative national estimates but the latter provides a more detailed estimate of costs. Differences in population size, methods and primary outcomes make it difficult to compare results. However, the estimated direct medical cost of RVGE hospitalization is over ranges from 1 million euros to >10 million euros

TABLE 1. Studies of Economic Burden of Rotavirus Gastroenteritis in Europe

Author	Country	Events Included	Costs Included	Key Findings	Comments
Cowden, ² 2001	Scotland	Hospitalizations	Medical	£275,000 to £835,000 direct medical cost per year for community-acquired RVGE; hospitalization	Based on national admissions and laboratory surveillance data. Cost based on average bed-day cost
Fruhwirth, ¹ 2001	Austria	Community-acquired hospitalizations and nosocomial infections	Medical, nonmedical direct, indirect	€7.2 million direct medical cost per year for community acquired RVGE; €6.2 million direct medical cost per year for NRV	Based on community cohort study
Gil, ³ 2004	Spain	Hospitalizations	Medical	€3.6 million direct medical cost per year for community-acquired RVGE; hospitalization	Based on national admissions and laboratory surveillance data. Cost based on average bed-day cost
Harrington, ⁴ 2003	Ireland	Community-acquired hospitalizations and nosocomial infections	Medical	€1216 medical cost per community-acquired hospitalization; €600 medical cost per NRV. NRV accounts for 32% of RVGE hospital cost	Prospective study in 2 pediatric hospitals
Johansen, ⁵ 1999	Sweden	Hospitalization	Medical	\$1.8–2 million direct medical cost per year for community-acquired RVGE hospitalization	Based on national admissions and laboratory surveillance data. Cost based on average bed-day cost
Noel, ⁶ 1994	England	Hospitalizations	Medical	Estimated £6.3 million direct medical cost per year in England and Wales	2 yr study of patients admitted to a pediatric hospital for RVGE
Piednoir, ⁸ 2003	France	Nosocomial infections	Medical	€1930 additional direct medical cost per NRV case	Case-control prospective study in one hospital. Cost of NRV based on additional days hospitalized
Takala, ⁹ 1998	Finland	All RVGE	Medical, nonmedical, and indirect	\$260.28 total cost per case of RVGE in placebo group. Direct medical costs account for 89% of costs in placebo group. 95% reduction in costs among vaccinated children	Costs estimated for placebo and vaccine arms of a RCT
Roberts, ⁷ 2003	England	Community, outpatient and hospitalized cases	Medical, nonmedical direct, indirect	£18.2 million per year total societal costs; £11.1 million per year productivity losses; £5.1 million per year direct medical cost	Estimates of costs from all intestinal infectious disease. Based on community cohort study

in a number of countries. Only the studies by Fruhwirth et al¹ and Roberts et al⁷ include an estimate of the indirect costs associated with time lost from work and other direct expenses for families. Studies that include these additional costs are using the societal perspective. Estimates of indirect costs require surveys of a representative sample of parents of children with RVGE of different severities. Fruhwirth estimated that these family expenses accounted for 12% (30 euros) of the total societal cost of a community-acquired rotavirus infection resulting in a medical visit, and Roberts et al estimate that 61% of all RVGE costs are indirect.

Other RVGE Costs. Although estimates of the costs of hospitalization for RVGE exist in a number of countries, several other types of RVGE cost-generating events are less well-studied. These events include outpatient visits, nosocomial infections, outbreaks in elderly care facilities and community-treated cases. To fully assess the economic burden of RVGE, it is important to consider the economic impact of these potentially important cost-generating events as well. The economic burden of nosocomial rotavirus infection is dealt with in the article by Gleizes et al¹⁰ in this supplement.

There are few studies of the costs of outpatient visits for RVGE, in part because of the lack of epidemiologic estimates of the incidence of outpatient visits. Roberts et al⁷ have estimated the costs of cases of intestinal infections (including RVGE) treated by general practitioners in England. In addition to estimating the costs of treatment, they also calculate the nonmedical direct costs for affected families and time lost from work. The same study also estimates the costs for community diarrheal cases that do not result in treatment at a formal facility. Although the average cost for these cases (all causes) may be relatively low (£34.31 per case, primarily from lost work), their cumulative costs on affected families (through over-the-counter medication, supplies and time lost from work) could be significant.

Several studies have documented that community-acquired hospitalization for RV can result in significant hospital-acquired cases among those children admitted for other causes. The estimation of the economic consequences of these infections is challenging.^{1,4,8} In addition to requiring the estimation of the number or rate of new RV cases, it is essential to estimate the additional health care resource costs (or others) associated with hospital-acquired RV infection, usually based on the estimated increase in length of stay. This is particularly challenging because children with longer stays are more likely to be affected, making it difficult to determine the extent to which the hospital-acquired infection causes an increase in stay (rather the reverse). Piednoir et al⁸ and Harrington et al⁴ estimated the additional costs by matching cases with control patients with similar characteristics in France and Ireland, respectively. In the former study, nosocomial RV (NRV) infection resulted in a mean excess stay of almost 5 days, with an associated direct medical cost of >1900 euros.⁸ In the study conducted in 2 pediatric hospitals in Ireland, it was estimated that NRV accounted for 27% of all RV hospitalizations (with a mean excess cost of 600 euros) and approximately one-fourth of all medical costs associated with RV hospitalization.⁴ Although both studies estimated the additional bed-days due to NRV through

matching of patients, they used a different approach to evaluate this end point. However, by matching patients at the time of developing the RV infection (rather than at initial admission),⁴ the possible biases related the possible association between the length of hospitalization and the risk of developing RVGE.

Several questions must be addressed to assess the relative quality of the studies aiming to assess the economic burden of RVGE. Is disease incidence based on representative national data or individual facilities? Are case definitions sufficiently including all events where RVGE results in increased resource utilization and cost? Are mean medical costs estimated accurately; in particular were the increases in resource utilization caused by RVGE (length of stay, diagnostics and medications) appropriately estimated? Are estimates of productivity losses and nonmedical direct costs based on a prospective sample of caregivers? These factors will affect the accuracy, representativeness and completeness of the estimates and often limit the significance of the studies.

Finally RV hospitalizations may have other costs associated with hospitalization that are difficult to quantify. To control hospital-acquired cases, infection control measures are typically instituted, although these costs may not be fully captured by per diem hospital charges. In addition to the costs associated with individual hospital acquired cases, Lopman et al¹¹ have shown that gastroenteritis outbreaks in hospital wards in England and Wales can generate costs as a result of units being closed to new admissions to control infections. In addition, the strong seasonality of RV infection (sometimes corresponding to the peak of respiratory syncytial virus as well) may require increased capacity in hospital wards that is otherwise underutilized.

One of the limitations of economic burden studies is that they often include only a portion of the total costs associated with RVGE. Important cost-generating events (Fig. 1), such as outpatient visits, cases seeking informal care and nosocomial cases, may be left out because of insufficient epidemiologic information. Similarly important cost categories (most notably productivity losses and nonmedical direct expenses) may be overlooked because of the methodologic difficulties in measuring them such as the need for prospective surveys of caregivers (Fig. 1). These factors can contribute to a systematic underestimation of the true cost of illness.

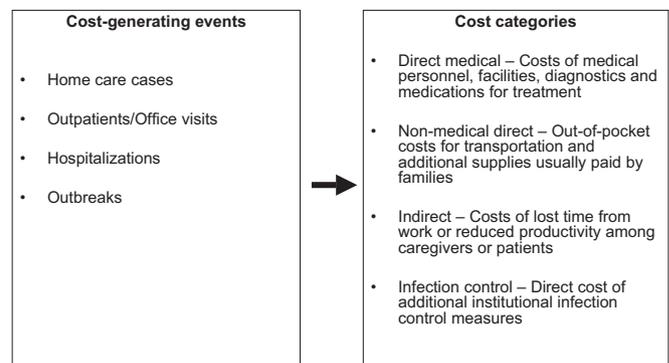


FIGURE 1. Cost-generating rotavirus events and cost categories.

ECONOMIC EVALUATION OF VACCINATION

Economic burden information is useful in describing the extent of RVGE as a problem for families, the health care system and society as a whole. However, additional information is needed to compare the costs and benefits of vaccination. Several approaches are used for economic evaluation of vaccines. They all provide a systematic way of comparing the net costs of vaccination with the expected benefits.

In general, there are 2 basic approaches. A “cost benefit” analysis compares the net monetary costs of vaccination with the net monetary benefits of vaccination. The results can be expressed as net costs or as the ratio of benefits to costs. On the other hand, in the “cost effectiveness” analysis, the incremental costs of vaccination are compared with the health gains (expressed as cases, lives saved or a health metric such as QALYs).

How would each be used to evaluate RV vaccination? The paper by Takala et al is the only published example of an economic evaluation of RV vaccination in a European setting.⁹ The study examines the economic outcomes observed in a clinical trial of the Rotashield® vaccine (Wyeth, Collegeville, PA) in Finland. The study included the medical, indirect and nonmedical direct costs of hospital and outpatient visits in the placebo and vaccine arms of the clinical trial. By comparing the costs for the 2 groups, they estimated the costs averted through vaccination. They found that the mean cost (direct and indirect) per child in the vaccinated group was \$0.72, compared with \$40.32 in the placebo group, demonstrating a significant reduction in the RV-related costs. They also estimated that at a cost of \$19.60 per child these averted costs would offset the cost of vaccination (break-even cost).⁹

A study by Tucker et al¹² in the United States took a similar approach but based the analysis on a model of the expected outcomes in an annual birth cohort, rather than the comparison of arms of a vaccine trial. The modeling approach used by Tucker et al¹² has the advantage of using representative epidemiologic, cost and efficacy data to estimate vaccine costs and benefits before the introduction of the vaccine. The advantage of the prospective approach used by Takala et al⁹ is that it allows for the estimation of actual costs of vaccinated and unvaccinated children. In addition, the Takala study includes empirical estimates of productivity losses while the paper by Tucker et al¹² does not.

Both types of cost benefit analysis that focus on the economic consequences of vaccination can be helpful to decision makers. If the costs of vaccination were less than medical costs averted, it would be cost-saving to the health care system, making it an excellent investment that saves money and improves health. If costs of vaccination were less than the societal costs averted (medical direct, nonmedical direct and indirect), then vaccination would make financial sense for society as a whole, although it may require a net investment from the health care system.

However, for the decision makers, the challenge arises when the costs of vaccination are greater than averted costs. This does not mean that vaccination is not appropriate but that societal and health care resources must be invested to

reduce the risk of infection and improve children’s health. As for most health interventions, a new approach does not need to be cost-saving to be cost-effective.

Cost benefit analyses can capture the expected reduction in RV morbidity and mortality resulting from vaccination. However, they do so by estimating the monetary value of these health improvements, based on either the human capital approach (lost productivity from premature mortality) or society’s willingness to pay to prevent a RV case or death. In practice, many decision makers are hesitant to use the approach of monetizing health gains.

Cost effectiveness analyses compare the net costs of vaccination (usually from the health care system perspective) to some measure of the health improvement from vaccination such as deaths averted, life-years saved or QALYs gained. This can be used to assess the efficiency of an intervention in obtaining a specific benefit or to assess the value of the intervention in relation to some standard of a “good investment.” Depending on the purpose, different health measures may be used. The cost per case avoided may be useful in comparing delivery strategies for the same vaccine (universal versus targeted). The cost per death averted or cost per life-year saved is often used to evaluate these vaccines for which the primary outcome is mortality reduction. However, when a vaccine is expected to reduce mortality and morbidity, some measure of improvement that captures both is required. QALYs are increasingly being used to evaluate vaccines and other interventions that reduce both morbidity and mortality. Studies that use QALYs as the main health outcome are often referred to as cost-utility analyses.

QALYs measure health based on the duration of time lived at different quality of life, using a 0–1 scale, in which 0 is death and 1 is perfect health. Mortality (or its prevention) is captured based on the duration of time and the quality of life that would have been experienced. Similarly morbidity is based on the reduction in quality and the duration of the event. Both are expressed as life-years. Although several approaches are used for estimating QALY weights, they are intended to reflect societal valuation of specific types of morbidity in comparison with changes in duration of life or a risk of death. As such, they provide a combined measure of mortality and morbidity that captures a wide range of vaccine benefits.

Several approaches are commonly used to estimate the QALY weight for a specific condition on the 0–1 scale. In direct elicitation studies, individuals with the condition (or those very familiar with it) are asked how they would trade off living with the condition and either a change in life expectancy (time tradeoff) or a risk of death (standard gamble). The second common approach is to use standardized health classification instruments. In this approach, respondents are asked to characterize a specific condition, based on specific health domains. For example, the EQ-5D¹³ instrument uses the domains of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. For each domain there are 3 levels of severity. An individual respondent can rank a condition by the level of each domain. A “score” is then based on standardized weights for each level, as determined in large population studies of preferences for the

different health states. Validated versions of the EQ-5D are available for most European countries. Other similar instruments include the Health Utilities Index (HUI; 3 versions). The advantage of these standardized health classification systems is that they generate comparable estimates for different conditions and are not prohibitively difficult to implement. The application of these methods to estimate QALYs associated with vaccine-preventable diseases is discussed in more detail below.

ECONOMIC EVALUATION OF OTHER VACCINES OR VACCINATION STRATEGIES IN EUROPE

Despite the lack of published economic evaluations of RV vaccination in Europe, evaluations of other vaccinations in Europe provide useful examples of the kinds of economic information that could help decision makers in weighing RV vaccination.

A number of studies use cost benefit analysis to compare the costs of vaccination to the averted costs resulting from vaccination.^{14–18} Many of the studies included both direct medical and indirect costs, allowing for the calculation of net benefits from the health care system and societal perspectives. Many of these studies also include additional analyses such as a cost-effectiveness analysis. For example, Asensi et al¹⁴ estimated that use of the 7-valent pneumococcal conjugate vaccine (PCV-70) in Spain would save a total of 81 million euros over 10 years, of which 43.5 million euros would be direct medical expenses. Vaccination would be cost-saving from the societal perspective (including productivity losses) at a cost per dose of <56.87 euros per dose.

A small group of studies include cost effectiveness analyses of bacillus Calmette-Guérin, influenza and hepatitis A and B vaccination that use cost per case or event averted.^{19–22} In most instances, these studies compare alternative vaccination targeting strategies to identify the most efficient strategy for preventing a specific outcome. For example, Hersh et al¹⁹ compare the cost effectiveness of universal versus targeted tuberculosis immunization in Finland, and Szucs et al²² compare the cost effectiveness of hepatitis A and B vaccination in different age groups in Germany. Vaccination of 11- to 15-year-olds was more cost-effective than vaccination of all children younger than 15 years of age.²² However, the limitation of the approach is that it does not allow evaluation of whether vaccination of younger children would also be a good health investment as a national strategy (even if it is not as cost-effective as vaccinating the older group).

Several studies evaluate vaccination cost effectiveness in terms of lives or life-years saved.^{14–16,23–30} This includes several studies of pneumococcal vaccines that focus on the health benefits associated with reduced mortality,^{14,16,23,25,27} as well as pertussis²⁹ and hepatitis B.²⁶ These analyses address vaccines that primarily affect mortality or focus only on the mortality impact of the vaccine. Extreme caution must be used in interpreting these results because they are not directly comparable. Studies differ by the age of the population studied and have been conducted in different country settings, which could affect vaccination effectiveness. In

addition, very different assumptions were used about vaccine prices directly affecting the cost effectiveness ratio. This precludes comparing the relative cost effectiveness of the different vaccines. In many cases, the vaccines being evaluated would also result in reductions in morbidity; however, these benefits would not be captured with lives or life-years saved as a measure of benefit.

A growing number of studies of the cost effectiveness of vaccination use QALYs as the measure of health benefit, allowing the consideration of both morbidity and mortality benefits of vaccination (Table 2). These include studies of pneumococcal vaccines^{23,25,30,33,35,38} as well as varicella,^{32,34} *Haemophilus influenzae* type b disease³⁶ and meningitis.^{28,40} In addition, several studies have assessed the QALY impact of specific vaccine-preventable diseases, such as meningitis.⁴⁰

Although these studies share the use of QALYs to capture morbidity and mortality prevention benefits of vaccination, they differ in several important ways (Table 2). Most notably, they differ in the way that QALY weights are determined. Assessing QALYs associated with vaccine-preventable illnesses in children by the usual methods described above is often challenging because of the age of the patients. Brisson and Edmunds³² estimate the QALY losses associated with varicella and the cost effectiveness of vaccination against it. In this study, parents of healthy children were asked to rate the health of a child with chickenpox using the HUI Mark 2 survey.⁴¹ QALY weights were calculated based on the standardized scoring algorithm that provides a score based on the combination of levels in each health domain and population based estimates of preferences for them.⁴¹ The QALYs lost for each condition were calculated by multiplying the change in QALY weight (compared with a healthy child) by the estimated duration of illness. Oostenbrink et al⁴⁰ use a similar approach to estimate the QALYs associated with meningitis symptoms using 3 health classification systems (EQ-5D and HUI Mark 2 and 3).^{13,41,42} A panel of pediatricians was asked to classify a variety of symptoms (deafness, mild hearing loss, epilepsy, mild mental retardation, severe mental retardation with tetraplegia, paresis of the leg and mild retardation with epilepsy and paresis) according to the questionnaires. QALY weights were calculated for each condition with the standardized scoring algorithms for each. The estimated QALY weights differed somewhat depending on which instrument was used. Each of the health classification systems use slightly different domains of health and thus are sensitive to different aspects of a condition. By use of alternative estimates of these weights, sensitivity analyses can determine the effect on the overall outcome.

The studies also differ in the types of nonfatal outcomes they consider. In particular, several studies only include severe long term health outcomes,^{22,31–33,35–39} whereas others also include short term transitory conditions.^{26,32,34,40}

In addition to providing decision makers with a method for comparing the cost effectiveness of different vaccines, a cost effectiveness analysis based on QALYs also provides a way to compare vaccines to decision makers' notions of how much they are willing to pay for a specific QALY improvement.

TABLE 2. Studies Using Quality-Adjusted Life Years (QALYs) to Evaluate Interventions Against Vaccine Preventable Diseases

Author	Vaccine Intervention	Country	Population	Outcomes Included	Method of QALY Estimation
Bos, ²³ 2003	Pneumococcal (7-valent)	Netherlands	Infants	Mortality, severe long term sequelae	Published estimates and author mapping to EQ-5D
Bos, ³¹ 2001	Pneumococcal (7-valent)	Netherlands	Infants	Mortality, severe long term sequelae	Published estimates and author mapping to EQ-5D
Brisson, ³² 2003	Varicella	England and Wales	Infants	Varicella, zoster	HUI Mark 2 in parents
De Graeve, ³³ 2000	Pneumococcal (23-valent)	Belgium	Elderly	Mortality, invasive pneumococcal disease	Published estimates and author assumptions
Edmunds, ³⁴ 2001	Herpes zoster	England and Wales	Various	Zoster	HUI Mark 2 in parents
Ess, ³⁵ 2003	Pneumococcal	Switzerland	Infants	Mortality, severe long term sequelae of meningitis	Literature, author assumptions
Livartowski, ³⁶ 1996	<i>Haemophilus influenzae</i>	France	Children	Permanent sequelae of Hib invasive disease	Expert opinion, and Gudex and Kind classification system
Melegaro, ²⁷ 2004	Pneumococcal	England and Wales	Infants	Mortality, hearing loss, seizures, bacteremia, pneumonia, otitis media	Published literature
Oostenbrink, 2002 ³⁷	Meningitis treatment	Netherlands	Children with meningeal signs	Mortality, long term sequelae	Published literature
Plans Rubio, ³⁸ 1995	Pneumococcal	Spain	Older than 5 yr old	Mortality, long term sequelae	Authors' assumptions
Ruedin, ³⁹ 2003	MenC and MenC/PCV-9	Switzerland	Various	Mortality, moderate and severe long term complications	Expert panel and HUI Mark 2
Oostenbrink, 2002 ⁴⁰	Meningitis diagnosis	Netherlands	Children with meningeal signs	Deafness, mild hearing loss, epilepsy mental retardation, paresis of the leg	EQ-5D, HUI Mark 2, HUI Mark 3 in pediatricians

Hib indicates *Haemophilus influenzae* type b; MenC, *Neisseria meningitidis* C.

EVALUATING THE HEALTH BENEFITS OF RV VACCINATION WITH QALYS

This growing literature on the cost effectiveness of vaccination based on QALYs has important implications for the consideration of RV vaccination in Europe. RV causes extensive short term morbidity, whereas the mortality (although very difficult to quantify) is probably very low in Western Europe but higher in Eastern European countries. Weighing the health benefits of vaccination against its costs requires a measure like QALYs that accounts for reductions in both morbidity and mortality.

There are several challenges to estimating the QALY impact of RVGE and the benefits of vaccination. The first is how to estimate the appropriate weight for a day with RVGE. There are no published empirically established values in Europe or elsewhere. A study by the United States Institute of Medicine used a QALY weight of 0.25 (on a scale of 0–1), based on authors' opinions rather than being empirically derived.⁴³ Developing empirical estimates of the quality of life impact of RVGE is particularly difficult because the affected children are typically too young to respond to surveys used to develop QALY weights.

Evaluation of varicella vaccination by Brisson and Edmunds³² and the Oostenbrink et al⁴⁰ study of meningitis use proxy assessments based on existing standard health status instruments, such as the EQ-5D and Health Utilities

Index. The studies used either parents or physicians as the respondents to assess a wide range of chronic and transitory conditions from chickenpox to hearing loss. The same approach could be used to assess the QALY weights for different severities of RVGE (hospitalization, outpatient visits and cases treated at home). For each severity level, parents and/or physicians could be asked to rate the child's health using one of the standardized instruments. Separate ratings could also be developed for children of different ages. The domains of health included in the instruments are intended to apply to a broad range of health outcomes and are not specific to RV or pediatric patients. However, the calculated QALY weights can be adapted to RV and adjusted by excluding irrelevant domains.

Although QALYs provide a useful measure that captures mortality and morbidity, they have several limitations in their application to childhood vaccines. Most notably, the diverse severity of illnesses and the fact that they occur in children make it difficult (if not impossible) to measure QALY weights in the most methodologically rigorous manner. This is also true for RV where several inherent limitations include the lack of an instrument designed specifically for pediatric applications and the common need to rely on proxy respondents. Nevertheless several things can be done to assess the internal validity of QALY estimates developed in this way. These include: comparing responses of different

proxy groups (parents and physicians); comparing the estimated weights based on clinical severity; and comparing estimates using multiple instruments. In the presence of this kind of uncertainty, economic analyses routinely use sensitivity analyses to determine the potential impact of these uncertain values on the robustness of the results. Using this approach, decision makers can include the morbidity reduction benefits of vaccination, without overstating them.

Although the QALY approach will remain subject to these uncertainties, it provides an important (albeit imperfect) measure of health benefit that decision makers can weigh against the net costs of vaccination in a specific country. Without a method for quantifying these nonfatal health benefits (such as the QALYs), economic evaluations of vaccination in low mortality settings will be based only on the financial costs and economic benefits. This underestimates the real public health benefit of morbidity-reducing vaccines such as those for RVGE, especially in wealthy settings, such as Europe. The methods for the economic evaluations of vaccines that reduce mortality and improve quality of life will continue to develop, and QALYs will continue to be an important tool for providing decision makers with quantifiable measures of health benefit that can be systematically compared with both costs and to other vaccinations.

REFERENCES

1. Fruhwirth M, Berger K, Ehlken B, et al. Economic impact of community- and nosocomially acquired rotavirus gastroenteritis in Austria. *Pediatr Infect Dis J*. 2001;20:184–188.
2. Cowden JM. An estimate of the costs of cases of rotavirus infection admitted to hospital in Scotland, 1997. *Health Bull (Edinb)*. 2001;188–192.
3. Gil A, Carrasco P, Jimenez R, et al. Burden of hospitalizations attributable to rotavirus infection in children in Spain, period 1999–2000. *Vaccine*. 2004;22:2221–2225.
4. Harrington M, Butler K, Cafferkey M. Rotavirus infection in hospitalised children: incidence and impact on healthcare resources. *Ir J Med Sci*. 2003;172:33–36.
5. Johansen K, Bennet R, Bondesson K, et al. Incidence and estimates of the disease burden of rotavirus in Sweden. *Acta Paediatr Suppl*. 1999;88:20–23.
6. Noel JS, Parker SP, Choules K, et al. Impact of rotavirus infection on a paediatric hospital in the east end of London. *J Clin Pathol*. 1994;47:67–70.
7. Roberts JA, Cumberland P, Sockett PN, et al. The study of infectious intestinal disease in England: socio-economic impact. *Epidemiol Infect*. 2003;130:1–11.
8. Piednoir E, Bessaci K, Bureau-Chalot F, et al. Economic impact of healthcare-associated rotavirus infection in a paediatric hospital. *J Hosp Infect*. 2003;55:190–195.
9. Takala AK, Koskeniemi E, Joensuu J, et al. Economic evaluation of rotavirus vaccinations in Finland: randomized, double-blind, placebo-controlled trial of tetravalent rhesus rotavirus vaccine. *Clin Infect Dis*. 1998;27:272–282.
10. Gleizes O, Desselberger U, Tatochenko V. Nosocomial rotavirus infection in European countries: a review of the epidemiology, severity and economic burden of the infection. *Pediatr Infect Dis J*. 2006;25:S12–S21.
11. Lopman BA, Reacher MH, Vipond IB, et al. Epidemiology and cost of nosocomial gastroenteritis, Avon, England, 2002–2003. *Emerg Infect Dis*. 2004;10:1827–1834.
12. Tucker AW, Haddix AC, Bresee JS, et al. Cost-effectiveness analysis of a rotavirus immunization program for the United States. *JAMA*. 1998;279:1371–1376.
13. Dolan P. Modeling valuations for the EuroQol health states. *Med Care*. 1997;35:1095–1108.
14. Asensi F, De Jose M, Lorente M, et al. A pharmacoeconomic evaluation of seven-valent pneumococcal conjugate vaccine in Spain. *Value Health*. 2004;7:36–51.
15. Coudeville L, Brunot A, Giaquinto C, et al. Varicella vaccination in Italy: an economic evaluation of different scenarios. *Pharmacoeconomics*. 2004;22:839–855.
16. Darkes MJ, Plosker GL. Pneumococcal conjugate vaccine (Pnevnar; PNCRM7): a review of its use in the prevention of *Streptococcus pneumoniae* infection. *Paediatr Drugs*. 2002;4:609–630.
17. Tormans G, Van Doorslaer E, van Damme P, et al. Economic evaluation of pertussis prevention by whole-cell and acellular vaccine in Germany. *Eur J Pediatr*. 1998;157:395–401.
18. Garpenholt O, Silfverdal SA, Levin LA. Economic evaluation of general childhood vaccination against *Haemophilus influenzae* type b in Sweden. *Scand J Infect Dis*. 1998;30:5–10.
19. Hersh AL, Tala-Heikkila M, Tala E, et al. A cost-effectiveness analysis of universal versus selective immunization with *Mycobacterium bovis* bacille Calmette-Guérin in Finland. *Int J Tuberc Lung Dis*. 2003;7:22–29.
20. Rajan E, Shattock AG, Fielding JF. Cost-effective analysis of hepatitis A prevention in Ireland. *Am J Gastroenterol*. 2000;95:223–226.
21. Scuffham PA, West PA. Economic evaluation of strategies for the control and management of influenza in Europe. *Vaccine*. 2002;20:2562–2578.
22. Szucs T. Cost-effectiveness of hepatitis A and B vaccination programme in Germany. *Vaccine*. 2000;18(suppl 1):S86–S89.
23. Bos JM, Rumke H, Welte R, et al. Epidemiologic impact and cost-effectiveness of universal infant vaccination with a 7-valent conjugated pneumococcal vaccine in the Netherlands. *Clin Ther*. 2003;25:2614–2630.
24. McIntosh ED, Conway P, Willingham J, et al. Pneumococcal pneumonia in the UK: how herd immunity affects the cost-effectiveness of 7-valent pneumococcal conjugate vaccine (PCV). *Vaccine*. 2005;23:1739–1745.
25. McIntosh ED, Conway P, Willingham J, et al. The cost-burden of paediatric pneumococcal disease in the UK and the potential cost-effectiveness of prevention using 7-valent pneumococcal conjugate vaccine. *Vaccine*. 2003;21:2564–2572.
26. Mangtani P, Hall AJ, Normand CE. Hepatitis B vaccination: the cost effectiveness of alternative strategies in England and Wales. *J Epidemiol Community Health*. 1995;49:238–244.
27. Melegaro A, Edmunds WJ. Cost-effectiveness analysis of pneumococcal conjugate vaccination in England and Wales. *Vaccine*. 2004;22:4203–4214.
28. Trotter CL, Edmunds WJ. Modelling cost effectiveness of meningococcal serogroup C conjugate vaccination campaign in England and Wales. *BMJ*. 2002;324:809.
29. Edmunds WJ, Brisson M, Melegaro A, et al. The potential cost-effectiveness of acellular pertussis booster vaccination in England and Wales. *Vaccine*. 2002;20:1316–1330.
30. Ament A, Baltussen R, Duru G, et al. Cost-effectiveness of pneumococcal vaccination of older people: a study in 5 western European countries. *Clin Infect Dis*. 2000;31:444–450.
31. Bos JM, Rumke HC, Welte R, et al. Health economics of a hexavalent meningococcal outer-membrane vesicle vaccine in children: potential impact of introduction in the Dutch vaccination program. *Vaccine*. 2001;20:202–207.
32. Brisson M, Edmunds WJ. Varicella vaccination in England and Wales: cost-utility analysis. *Arch Dis Child*. 2003;88:862–869.
33. De Graeve D, Verhaegen J, Ament A, et al. Cost effectiveness of vaccination against pneumococcal bacteremia in the elderly: the results in Belgium. *Acta Clin Belg*. 2000;55:257–265.
34. Edmunds WJ, Brisson M, Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. *Vaccine*. 2001;19:3076–3090.
35. Ess SM, Schaad UB, Gervaix A, et al. Cost-effectiveness of a pneumococcal conjugate immunisation program for infants in Switzerland. *Vaccine*. 2003;21:3273–3281.

36. Livartowski A, Boucher J, Detournay B, et al. Cost-effectiveness evaluation of vaccination against *Haemophilus influenzae* invasive diseases in France. *Vaccine*. 1996;14:495–500.
37. Oostenbrink R, Oostenbrink JB, Moons KG, et al. Cost-utility analysis of patient care in children with meningeal signs. *Int J Technol Assess Health Care*. 2002;18:485–496.
38. Plans Rubio P, Garrido Morales P, Salleras Sanmarti L. The cost-effectiveness of pneumococcal vaccination in Catalonia. *Rev Esp Salud Publica*. 1995;69:409–417.
39. Ruedin HJ, Ess S, Zimmermann HP, et al. Invasive meningococcal and pneumococcal disease in Switzerland: cost-utility analysis of different vaccine strategies. *Vaccine*. 2003;21:4145–4152.
40. Oostenbrink R, Moll HA, Essink-Bot ML. The EQ-5D and the Health Utilities Index for permanent sequelae after meningitis: a head-to-head comparison. *J Clin Epidemiol*. 2002;55:791–799.
41. Torrance G, Feeny D, Furlong W. Multiattribute utility function for a comprehensive health status classification system: Health Utilities Index Mark 2. *Med Care*. 1996;34:702–722.
42. Furlong W, Feeny D, Torrance G, et al. Multiplicative multi-attribute utility function for the health utilities index Mark 3 (HUI3) system: a technical report. In: *McMaster University Centre for Health Economics and Policy Analysis working paper*: 1998:98–111.
43. Institute of Medicine. *Vaccines for the 21st Century: a Tool for Decision-Making*. Washington, DC: National Academies Press; 1999.