Pharmacoeconomic Analysis of Vaccination in Developed Versus Developing Countries

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Abstract

Pharmacoeconomic analyses are performed preferentially in developed countries where there is an imperative to obtain "value for money" and to achieve cost-effectiveness. Such analyses are performed in low-income/developing countries and middle-income countries, partly to save scarce resources but also to improve the overall economic outlook, promote productivity gains, and foster further investment in vaccination. Analyses appear to be performed preferentially for therapeutic products as opposed to vaccines, but this may change as the impact of applying the results of pharmacoeconomic analyses of vaccines are measured and quantified. *(J Pediatr Inf 2014; 8: 110-20)*

Keywords: Pharmacoeconomic analysis, vaccination, developing countries

Introduction

Are pharmacoeconomic analyses performed preferentially in developed countries? If they are, is this because there is a greater desire to obtain "value for money" in developed countries as opposed to developing countries? Should it not be the other way around? Are such analyses performed preferentially for therapeutic products as opposed to vaccines? Are the results of such analyses more impactful in developed or in developing countries? These and other questions will be addressed by this review of published studies performed over the last 2 decades.

As implied above, the impact of favorable (or unfavorable) pharmacoeconomic analyses can be enormous, in that they are used to guide decision-making. Perhaps the most striking example of this impact (in developed countries) is that of the UK National Institute for Health and Care Excellence (NICE), where guidance is based on measures, such as quality-adjusted life-years, where randomized controlled clinical trials are used as the benchmark if possible and where modeling is performed and thresholds are set.

Similar health technology assessment exercises are performed in many other developed countries, such as the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, the Canadian Agency for Drugs and Technologies in Health (CADTH), the Scottish Medicines Consortium (SMC), and the Zorg Instituut Nederland (Care Institute NL). In fact, the European Medicines Agency works closely with the European Network for Health Technology Assessment (EUnetHTA), although pharmacoeconomic analyses are still generally a national issue. Despite the relative sophistication of the drug reimbursement decision-making processes in countries of the Organisation for Economic Co-operation and Development (OECD), one health policy analysis reported that only 5 of 33 OECD countries (Ireland, Norway, Portugal, Slovak Republic, and Slovenia) had fully transparent systems, using both clinical and cost-effectiveness evidence, and have a formal appeal mechanism to a separate committee from that that made the first decision (1). Notably, it is the latter that is lacking in countries, such as England, Scotland, and the Netherlands.

Responding to the perceived need for health technology assessment exercises to be performed in developing countries, the Health

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Technology Assessment International Interest Sub-Group on Developing Countries (HTAi DC ISG) was launched in 2008. Furthermore, it is being recognized that health technology assessments will play an increasing role in the future development of the healthcare sector in countries, such as India (2), and international organizations, such as the Pan American Health Organization, have been instrumental in defining health technology assessment methodologies suitable for developing countries (3). We caution, however, that published state-of-the-art health economic research can be misleading. Correspondence regarding how health economic research is represented from South Africa (4) draws attention to the shortcomings of what is purported to be a systematic review of health economic research in South Africa (5).

The purpose of this review is to compare and contrast pharmacoeconomic analyses in developing and developed countries.

Material and Methods

Medline searches were performed, covering the period from 1996 to June 2014, using the terms "pharmacoeconomics" or "pharmaceutical economics" and "vaccines" or "immunization" (search A), and for the period from 2013 to June 2014 using the terms "cost-benefit analysis" or "cost-effectiveness" and "vaccines" or "immunization" (search B). A third search was performed to help answer the question about pharmacoeconomic analyses in therapeutics as opposed to vaccines, for the period from 2013 to June 2014 simply using the term "pharmacoeconomics" (search C). No language or country restrictions were imposed. No unpublished studies were sought. Papers were considered relevant if there was an attempt to quantify cost-benefit, cost-utility, cost-effectiveness or cost-minimization and/or if there was an attempt to gather data for such purposes.

Results

Search (A) yielded 40 citations, of which 27 were relevant (Table 1). Search (B) yielded 150 citations, of which 86 were relevant (Table 2). Only one citation (6) was common to both searches.

There were 20 studies (17% of a total of 112) devoted to developing (low-income) countries (see Tables 1 and 2 for references). Five deal directly with African countries: a malaria vaccine for sub-Saharan Africa, a rotavirus vaccine for Ethiopia (grouped with India), a rotavirus vaccine for Malawi, a pneumococcal conjugate vaccine for Kenya, and a measles vaccine for South Africa. Four deal with India: one study addressing all vaccines, one addressing rotavirus (the one grouped with Ethiopia), and two addressing Hib. While Brazil and Mexico are otherwise grouped with "middle-income countries," other Latin America countries are represented by 9 studies: pneumococcal conjugate vaccine (6), human papilloma virus (HPV), rotavirus vaccine [2 grouped with pneumococcal vaccine (PCV)], the expanded program on immunization (EPI) (1), Hib (1 grouped with PCV and rotavirus), and varicella. Three remaining studies cover HPV in all developing countries (7), vaccines for neglected diseases in Advance Market Commitment countries (8), and the measles/rubella vaccine as part of the Global Vaccine Action Plan (9).

Regarding middle-income countries, there were 14 studies (Tables 1, 2) <: PCV in Turkey, Mexico, and Thailand; 2 studies on Hib; 3 studies on HPV (including 1 in Malaysia); 1 study on meningococcal conjugate vaccine in Brazil; 1 on rotavirus vaccine in Indonesia; 2 studies on dengue vaccine in Brazil; and 1 study each on hepatitis A virus vaccine and influenza vaccine.

There were 13 studies that took a "global" perspective (Tables 1, 2): not surprisingly, influenza vaccination was represented by 4 studies; varicella and HPV were represented by 2 each; rotavirus vaccine, poliomyelitis vaccine, and rubella vaccine were represented by 1 each; and 2 studies addressed "all" vaccines (10, 11).

The remaining 75 studies were thus directed towards analyses performed in developed countries (Tables 1, 2). These consisted of: 10 each for pneumococcal conjugate vaccine and human papillomavirus vaccine; 9 each for rotavirus vaccine and influenza vaccine; 7 for pertussis or Tdap; 5 for varicella vaccine; 4 each for meningococcal vaccine and HBV vaccine; 3 each for MMR and "all" vaccines; and 1 each for respiratory syncytial virus (RSV) vaccine, "varicella/pneumococcal/pertussis/HAV in the elderly," and for vaccine barcodes" (the total adds up to more than 75, because several studies covered more than 1 vaccine).

Search (C) produced 125 studies (in any country) of relevance: 3 relating to vaccines, 83 relating to specific therapeutic areas, and 39 relating to "generic" aspects of pharmacoeconomic analyses (Table 3).

Discussion

The main observation is that a wide variety and breadth of vaccines have been studied in all age groups and in many countries. There are relatively few analyses (17%) directly related to developing countries. The possible reasons may be the lack of reliable input data (12) or the lack of resources to provide the vaccine, even if it was shown to be cost-effective (13). Even so, when pharmacoeconomic studies are performed, as for example in

Table 1. Search result (A) "pharmacoeconomics" or "pharmaceutical economics" and "vaccines" or "immunization" (1996 to June 2014): citations of relevance

Vaccine	Journal	Year	Country	Author
Pneumococcal conjugate	Value in Health	2012	Turkey	Turel O (6)*
Rotavirus	Drugs in R&D	2012	"Developed" countries	Plosker GL (35)#
HPV	Value in Health	2012	Taiwan	Demarteau N (36)#
HPV	Value in Health	2012	"Developing" countries	Termrungruanglert W (7)$
Pneumococcal conjugate	Value in Health	2012	Taiwan	Wu DB (37)#
Malaria	Value in Health	2011	Sub-Saharan Africa	Maire N (28)$
Men C conjugate	Value in Health	2011	Brazil	de Soarez PC (38)*
Seasonal flu	Value in Health	2011	USA	Clements KM (39)#
Pneumococcal conjugate	Vaccine	2011	Latin America	Giglio N (40)$
Pneumococcal conjugate	Value in Health	2011	Mexico	Mucino-Ortega (41)*
Seasonal flu	Value in Health	2011	USA	Prosser LA (42)#
HPV	J Clinical Pharmacy and Therapeutics	2011	Global	Pomfret TC (43)&
HPV	Asian Pacific J of Cancer Prevention	2010	Malaysia	Ezat WP (24)*
HPV	J Managed Care Pharmacy	2010	USA	Armstrong EP (44)#
Hib	Expert Rev of Pharmacoeconomics and Outcomes Research	2009	Low and middle income countries	Griffiths UK (45)*
Target vaccines	J Managed Care Pharmacy	2007	Global	Armstrong EP (10)&
Neglected diseases	Health Economics	2007	Advance Market Commitments	Berndt ER (8)$
Influenza	Vaccine	2006	25 EU countries	Ryan J (46)#
Meningococcal B and pneumo	Pharmacoeconomics	2006	Netherlands	Bos JM (47)#
Rotavirus	PIDJ	2006	Europe	Rheingans RD (48)#
Varicella	Pharmacoeconomics	2004	Germany	Hammerschmidt T (49)#
Pneumococcal conjugate	Expert Review of Vaccines	2003	Netherlands	Postma MJ (50)#
Varicella	Pharmacoeconomics	2003	Global	Thiry N (51)&
Influenza	Drugs	2002	Global	Postma MJ (52)&
Acellular pertussis	Pharmacoeconomics	2001	Canada	Iskedjian M (53)#
Influenza	Drugs and Aging	2000	Global	Postma MJ (54)&
Rotavirus	Annals of Pharmacotherapy	1999	Global	Wandstrat TL (55)&

*: Middle income countries
#: Developed countries
$: Developing countries
&: Global
HPV: the human papilloma virus

a study of medications at two tertiary care hospitals in Pakistan, one of the stated reasons for performing the study was "to save economic resources" (14). However, in a study on the prevention of cervical cancer in the Brazilian Amazon region, which, for the purposes of this paper, was classified as "developing," the authors conclude that HPV vaccination "has a favorable profile in terms of cost-utility, and its inclusion in the immunization schedule would result in a substantial reduction in incidence and mortality" (15). This is similar to the conclusion drawn in a study of the introduction of pneumococcal conjugate vaccine in Kenya, which would be "highly cost-effective from a societal perspective" (16), and of Hib conjugate vaccine in India, which would also be cost-effective (17).

One novel solution is proposed in the *application* of cost-effectiveness analyses in developing countries,

Table 2. Search result (B) "cost-benefit analysis" or "cost-effectiveness" and "vaccines" or "immunization" (2013 to June 2014): citations of relevance

Vaccine	Journal	Year	Country	Author
HPV	Vaccine	2013	Israel	Ginsberg GM (56)#
HAV	Expert Review of Vaccines	2013	Middle-income countries	Suwantika AA (22)*
Pertussis	Vaccine	2013	Netherlands	Lugner AK (57)#
Rotavirus	Vaccine	2013	Taiwan	Chang WC (58)#
Influenza	Vaccine	2013	Global	Peasah SK (59)&
Influenza	Human Vaccines and Immunotherapeutics	2013	Low and middle income countries	Ott JJ (23)*
Tdap	PLoS ONE	2013	USA	McGarry LJ (60)#
Measles and rubella	Bundesgesundheaitsblatt, Gesundheitsforschung, Gesundheitsschutz	2013	Germany	Wichmann O (33)#
Measles and rubella	Vaccine	2013	Global Vaccine Action Plan	Thompson KM (9)$
HPV	Revista Da Associacao Medica Brasileira	2013	Brazilian Amazon	Fonseca AJ (15)$
Meningococcal B	Human Vaccines and Immunotherapeutics	2013	Netherlands	Pouwels KB (61)#
HBV	Human Vaccines and Immunotherapeutics	2013	Italy	Boccalini S (26)#
All	Human Vaccines and Immunotherapeutics	2013	Global	Postma MJ (11)&
Rotavirus	Journal of Medical Economics	2013	Japan	Itzler R (62)#
HPV	Human Vaccines and Immunotherapeutics	2013	France	Bresse X (63)#
Seasonal influenza	Human Vaccines and Immunotherapeutics	2013	UK	Jit M (64)#
Varicella	Human Vaccines and Immunotherapeutics	2013	Belgium	Bilcke J (65)#
HPV	Vaccine	2013	Canada	Brisson M (66)#
HPV	Vaccine	2013	Low and middle income countries	Fesenfeld M (13)*
HPV	Vaccine	2013	Netherlands	Luttjeboer J (67)#
Pneumococcal conjugate	Vaccine	2013	USA	Smith KJ (68)#
Dengue	Vaccine	2013	Brazil	Durham DP (29)*
HPV	Vaccine	2013	Belgium	Demarteau N (69)#
HBV	Vaccine	2013	USA	Kuan RK (70)#
All available	Vaccine	2013	Spain	Cortes I (71)#
HPV	International J of Cancer	2014	Canada	Drolet M (72)#
Rotavirus	Vaccine	2013	India and Ethiopia	Verguet S (18)$
HBV	Pediatrics	2014	USA	Barbosa C (27)#
RSV	Vaccine	2013	USA	Regnier SA (31)#
Dengue	Seminars in Immunology	2013	Brazil	Barnighausen T (30)*
Avian influenza	Biosystems	2013	USA	Agusto FB (73)#
All	Indian J Medical Ethics	2013	India	Jayakrishnan T (12)$
Rotavirus	Tropical Medicine and International Health	2014	Malawi	Madsen LB (19)$
Pertussis	Vaccine	2013	Japan	Itatani T (74)#
HPV	BMC Infectious Diseases	2013	Estonia	Uuskula A (75)#
Pneumococcal conjugate	Vaccine	2013	Thailand	Kulpeng W (76)*
MMR	Occupational Medicine	2013	UK (healthcare workers)	Giri P (77)#
Pneumococcal conjugate	Vaccine	2013	Japan	Hoshi SL (78)#
Pneumococcal conjugate	BMC Public Health	2013	Peru	Gomez JA (79)$
Measles	Vaccine	2013	Rep. of Korea	Bae GR (32)#

Table 2. Search result (B) "cost-benefit analysis" or "cost-effectiveness" and "vaccines" or "immunization" (2013 to June 2014): citations of relevance (continued)

Vaccine	Journal	Year	Country	Author
MenB	Vaccine	2013	UK	Christensen H (80)#
Varicella, pneumo, pertussis, HAV	BMC Geriatrics	2013	Netherlands	Eilers R (81)#
Rotavirus, pneumococcal	Vaccine	2013	Colombia/global	de la Hoz-Restrepo F (82)$
EPI	Vaccine	2013	Colombia	Castaneda-Orjuela C (20)$
Pneumococcal conjugate	Vaccine	2013	Latin America and Caribbean	Bahia L (83)$
Hib, pneumo, rotavirus	Vaccine	2013	Latin America, global	Clark A (84)$
Rotavirus, pneumococcal	Vaccine	2013	Latin America	de Oliveira LH (85)$
Influenza	Vaccine	2013	USA	Yoo BK (86)#
Rotavirus	Vaccine	2013	Indonesia	Suwantika AA (87)*
Vaccine barcode	Vaccine	2013	USA	O'Connor AC (88)#
Pneumococcal conjugate	PLoS ONE	2013	Kenya	Ayieko P (16)$
Poliomyelitis	Philosophical Transactions of the Royal Society of London	2013	Global	Barrett S (89)&
Varicella	Expert Review of Pharmacoeconomics and Outcomes Research	2013	France	Bresse X (90)#
Tdap	Vaccine	2013	USA	Ding Y (91)#
Meningococcal	PLoS ONE	2013	Netherlands	Hepkema H (92)#
Pneumococcal conjugate	Journal of the Formosan Medical Association	2013	Taiwan	Wu DB (93)#
Pneumococcal and influenza	American Journal of Managed Care	2013	USA	Lin CJ (94)#
Hib	Health Policy & Planning	2013	India	Gupta M (17)$
Pneumococcal	Value in Health	2013	Turkey	Turel O (6)*
Pneumococcal conjugate	Pediatrics	2013	USA	Stoecker C (95)#
Hib	Journal of Pediatrics	2013	India	Clark AD (96)$
Hib	Journal of Pediatrics	2013	Low- and middle-income	Griffiths UK (97)*
Tdap	Pediatrics	2013	USA	Terranella A (98)#
Rotavirus	BMC Medicine	2013	Netherlands	Bruijning-Verhagen P (99)#
All and HPV	Expert Review of Vaccines	2013	Europe, Netherlands	Postma MJ (100)#
Rubella	BMC Public Health	2013	Global	Babigumira JB (101)&
Influenza	BMC Infectious Diseases	2013	Global	Kelso JK (25)&
Pneumococcal conjugate	American Journal of Preventive Medicine	2013	USA	Smith KJ (102)#
All	Vaccine	2013	Spain	Garcia-Altes A (103)#
Varicella	Vaccine	2013	USA	Goldman GS (104)#
Measles	Global Health Action	2013	South Africa	Verguet S (34)$
Rotavirus	Asia Pacific Journal of Public Health	2013	Korea	Kang HY (105)#
HPV	BMC Medicine	2013	Low- and middle-income countries	Jit M (106)*
Rotavirus	Annali di Igiene	2013	Italy	Vitale F (107)#
HPV	BMC Infectious Diseases	2013	Netherlands	Westra TA (108)#

Table 2. Search result (B) "cost-benefit analysis" or "cost-effectiveness" and "vaccines" or "immunization" (2013 to June 2014): citations of relevance (continued)

Vaccine	Journal	Year	Country	Author
Pneumococcal conjugate	Clinical Therapeutics	2013	Denmark and Sweden	Klok RM (109)#
Influenza	BMC Infectious Diseases	2013	Belgium	van Vlaenderen I (110)#
Varicella	Vaccine	2013	Netherlands	de Boer PT (111)#
Rotavirus	BMC Infectious Diseases	2013	Netherlands	Tu HA (112)#
Pertussis	Vaccine	2013	Italy	Meregaglia M (113)#
Varicella	Pharmacoeconomics	2013	Global	Szucx TD (114)&
HPV	Clinical Obstetrics and Gynecology	2013	Global	Esselen KM (115)&
Rotavirus	PLoS ONE	2013	Belgium	Standaert B (116)#
Influenza	Vaccine	2013	UK	Pitman RJ (117)#
Varicella	Vaccine	2013	Colombia	Paternina-Caicedo A (118)$
HBV	Diabetes Care	2013	USA	Hoerger TJ (119)#

*: Middle income countries
#: Developed countries
$: Developing countries
&: Global
HPV: the human papilloma virus; HAV: hepatitis A vaccination; EPI: the expanded programme on immunization; HBV: hepatitis B vaccination; MMR: measles, mumps, and rubella

using the example of rotavirus vaccination in India and Ethiopia (18). The authors propose that incorporating financial risk protection and distributional consequences across the whole wealth strata of the country into the economic evaluation of vaccine policy enables "selection of vaccine packages based on the quantitative inclusion of information on equity and on how much financial risk protection is being bought per dollar expenditure on vaccine policy, in addition to how much health is being bought." Another rotavirus example, this time from Malawi, noted that the cost of implementation would be high when compared with the government health budget per capita and that new financing opportunities were necessary (19). A study on the cost of the Colombian Expanded Program on Immunization proposes using standardized tools to improve cost data for program planning (20).

A number of studies have been performed in the following middle-income countries: Turkey, Mexico, Thailand, Malaysia, Brazil, and Indonesia. By contrast with the stated reasons for performing such studies in developing countries, it is more likely that the reasons for performing them in middle-income countries are to improve the overall economic outlook, promote productivity gains, and foster further investment in vaccination (21). A review of economic evaluations of hepatitis A virus vaccination in middle-income countries suggests that such vaccination could be cost-saving (22), while a Turkish study, highly populated with local data, suggests that pneumococcal conjugate vaccination in Turkey would be very cost-effective as an intervention (6). Another review of the economic evaluation of influenza vaccination in middle-income countries came to the conclusion that in middle-income countries, "influenza vaccination provided value for money for elderly, infants, adults, and children with high-risk conditions" (23). However, the authors went on to note that "serious methodological limitations do not allow drawing conclusions on cost-effectiveness of influenza vaccination in middle-income countries" and that "evidence on cost-effectiveness from low-income countries is lacking altogether."

We caution, however, that the published state-of-the-art health economic research can be misleading. In correspondence regarding how health economic research is represented from South Africa, the authors Gow et al. (4) draw attention to the shortcomings of what is purported to be a systematic review of health economic research in South Africa (5).

The analyses performed in developed countries are most likely performed to minimize costs to the healthcare system in exchange for the maximum benefit and/or define a level of cost-effectiveness. An in-depth examination of economic evaluations of vaccines in Europe was performed by Postma et al. (11), citing the need for models to be, at times, rather complex.

Regarding the imbalance in published studies-there being more studies addressing therapeutic areas rather than vaccines-this is partly due to the larger number of

Table 3. Search result (C) "pharmacoeconomics (2013 to June 2014)

Therapeutic area	Number of studies
Oncology	27
Immunology/rheumatology	12
Cardiology	9
Analgesia/anaesthesia	4
Psychiatry	4
Diabetes	3
Haematology	3
Hepatitis C virus	3
Orphan drugs	3
Vaccines	3
Urology/renal	2
Alzheimer	2
Gastroenterology	2
Respiratory/rhinosinusitis	2
Epilepsy; STDs; osteoporosis; invasive fungal disease; Chinese medicines; generics; Caesarian Section	1 each
TOTAL	86
"Generic" aspects of pharmacoeconomic analyses	
Health state valuation	7
Personalised medicine	5
Pricing	4
Pharmacoeconomic education; survival analysis; heterogeneity of treatment; diagnostics/biomarkers; early scientific advice; psychosocial/behaviour	2 each
Questionnaires; budget impact analysis; OTC switch; patient adherence; prescription database; formularies; social interaction systems; risk sharing; law; comparative effectiveness; new technologies	1 each
TOTAL	39

therapeutic medicines as opposed to prophylactic vaccines and partly due to the sometimes very expensive costs of some therapeutics. But, it is the imbalance within "therapeutic" studies that is also notable-there being a predominance of studies in oncology, immunology, and rheumatology. Again, this is likely to be due to the sometimes very expensive costs in these therapeutic areas and the need to provide justification for using healthcare resources in these areas.

There are some attempts to look into the future-prophylaxis of HPV to prevent future cervical cancer in low- and middle-income countries (13, 24), severity-based analyses for influenza pandemics (25), prophylaxis of HBV to prevent future hepatocellular carcinoma (22, 26, 27) and there are also attempts to look at vaccines under development: malaria (28), dengue (29, 30), and RSV (31). There are also a few studies looking at the potential for the "elimination" of measles (9, 32-34).

What is clear is that pharmacoeconomic analyses have been performed and continue to be performed when new vaccines appear, when "old" vaccines are studied in new situations, and when economic predictions need to be made to direct resource allocation. While there is a relative paucity of analyses in low-income/developing countries and a relative paucity of data to be inserted into the models, those analyses performed in these situations are helpful in guiding policy decisions. One hesitates to recommend standardization because of the great heterogeneity between low-income/developing countries themselves and between them and middle-income and developed countries. Nevertheless, a degree of cross-country and cross-regional cooperation would be helpful.

Conclusion

Pharmacoeconomic analyses are performed preferentially in developed countries, where there is an imperative to obtain "value for money" and to achieve cost-effectiveness. Such analyses are performed in low-income/developing countries and middle-income countries partly to save scarce resources but also to improve the overall economic outlook, promote productivity gains, and foster further investment in vaccination. Analyses appear to be performed preferentially for therapeutic products as opposed to vaccines, but this may change, as the impact of applying the results of pharmacoeconomic analyses of vaccines are measured and quantified.

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