

Health Technology Assessment and vaccine: new needs and opportunities?

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Abstract

Health Technology Assessment (HTA) can represent an innovative and effective approach to supply decision-makers with a valid instrument to improve the allocation of resources in the field of vaccines.

We proposed a HTA approach for considering the introduction of a new vaccine that could potentially have a great impact on the population's health, using as an example the vaccine against Human Papilloma Virus (HPV). This approach could be of great interest when the decision making process involves choices regarding new vaccines.

We developed a HTA approach for assessing all of the aspects involved in the introduction of vaccines against HPV in Italy, considering the following issues:

- epidemiological evaluation of HPV infection and related pathologies through the consultation of data banks and the scientific literature;
- evaluation of health care resources utilisation by people suffering from the infection/ related diseases, through the consultation of hospital archives;
- systematic review and meta-analysis of randomised clinical trials on HPV vaccination effectiveness and safety;
- mathematical modelling and economic evaluation of the vaccination using a cost-effectiveness analysis;
- evaluation of the impact of vaccination on the Health System [organisational aspects, vaccine surveillance, relationship between different decisional levels (national, regional)];
- analysis of the ethical, social (acceptability, availability, accessibility, information) and legislative aspects of vaccination.

A HTA report on the new vaccine could represent an new important tool to support the choice of decision makers in order to better inform the allocation of economic resources and maximize healthcare services, since it takes into account not only the burden and the epidemiology of the disease, and the economic evaluation of different scenarios, but also the social, legal and bioethical aspects.

For HTA to support the introduction of new technologies, and new vaccines can be considered in this sense, there to utilise a process that is well defined, transparent and widely used.

Key words: Health Technology Assessment, vaccines, meta-analysis, economic evaluation, epidemiology, ethics

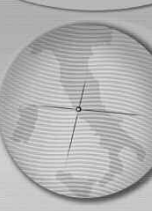
Introduction

Health Technology is an internationally recognised term that covers any instrument, device and method used to promote health, prevent and treat diseases and improve rehabilitation or long-term care. Technologies, in this context, are not restricted to new drugs or pieces of sophisticated equipment, but include procedures, care settings and screening programmes. Technologies can improve health conditions but also result in a continuous increase in health care costs.

Today one of the most important problems in Public Health is the challenge of reducing the

global mortality from infectious diseases; as they are still responsible for about 25% of global mortality, especially in children aged younger than 5 years [1]. In particular, the development and the spread of vaccine use has made an important contribution to the control of infectious diseases, reducing incidence and mortality, as shown by the success of smallpox eradication and the reduction of the measles mortality rate [2].

Over the past two decades, scientific progresses have opened the way to the development of new prophylactic vaccines against many acute infectious diseases [3]. The introduction of new



vaccines will then represent a central issue for decision makers, because of the large number of vaccines that will be available by 2015 [4].

However, since healthcare economic resources are limited, it will not be possible for Governments to finance all vaccines produced by medical industries and it will be necessary to decide how to allocate resources, according to the populations' needs [5]. For this reason, Health Organizations now need an instrument that will let them appraise not only the validity and the safety of medical technologies but also their efficiency, appropriateness and costs [6].

Currently, the practice of good decision-making is based on evidence based medicine and cost-effectiveness evaluation of the introduction of new vaccines in a specific context. Nonetheless, political choices are influenced by a series of other structural, organizational and legal factors, such as the type of health system (public-private and/or mixed), the legislative aspects (compulsory or recommended vaccination) and the decisional levels (super-national, national, regional, local).

In this multifaceted context Health Technology Assessment (HTA) can represent an innovative and effective approach in order to supply decision-makers with a valid instrument to better allocate resources.

HTA developed in '70 as a discipline that gives a systematic method of evaluation of alternative technologies, both on the clinical and the economic point of view [7]. The HTA can be defined as a multidisciplinary instrument of search that aims to examine the clinical (effectiveness, emergency, indications of use), economic, organizational, ethics, juridical, social and cultural implications of the spread and the use of specific biomedical technologies [8]. Therefore, we can consider HTA as a discipline that estimates not only the effectiveness and the efficiency of the technologies, but also their wider impact on the population [8].

HTA is a bridge between the world of research and the world of decision-making, in particular, policy-making [9].

Using different operative methods, HTA scientifically supports different decisional levels: political decision-makers (macro level); financing bodies of new technologies (meso level); clinical decisions (micro level).

The HTA process consists of two phases: the first is based on a systematic review and Evidence Based Medicine whereas the second phase consists of the synthesis of evaluation findings and in the formulation of conclusions and recommendations, based on the data gathered from the scientific literature. Because Health Technology Assessment is

interdisciplinary, it relies on various types of evidence, including links with investigators, governments, health care organizations and other payers, patients, industry and the media [9, 10].

Based on these considerations, could a HTA approach be useful to vaccines? In order to determine if this relationship already existed, we undertook a search of the PubMed database using the words "health technology assessment" AND "vaccine". Very few abstracts of papers appeared, and all of them refer to a systematic review or an economic evaluation (preferably cost-effectiveness analysis). However HTA provides a different approach to a specific health issue.

In this sense, since the relationship between HTA and vaccines is not actually well developed, the aim of this paper is to highlight the items that should be addressed through a Technology Assessment perspective with regards to vaccines.

The HTA framework applied to vaccine

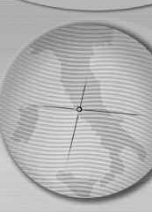
The implementation of a HTA report on a specific vaccine faces several methodological problems, including the setting (a specific nation, a specific continent or the entire world), temporal consideration and the vaccination target population.

We developed a possible framework for HTA with regards to a generic vaccine, which could then be specifically modified for a specific vaccine for an infectious disease.

A possible structure of this procedure is as follows:

1. Evaluation of the epidemiology of disease/infection;
2. Investigation of the disease burden in different countries (hospitalisations, excess death, etc.);
3. Studies of the current treatment practices of the disease/infection, of the preventive measures to avoid infection (immunisation, evidence of immunisation, immunisation in practice) and of the adverse effects of immunisation;
4. Elaboration of a mathematical model predicting epidemiological and economical impact of vaccination;
5. Economic evaluation of immunisation by means of a cost-benefit and a cost-effectiveness analyses;
6. Investigation of biotechnological aspects and manufacturers view;
7. Evaluation of ethical, legal and social issues of the infection and related diseases;
8. Study of the organisational aspects and of the impact of vaccination on the health system.

In this paper the rationale of part of this framework is described, along with an example of a possible HTA report for a specific vaccine.



Epidemiological impact of vaccines on populations

Public Health decisions for the introduction of new vaccines and new technologies have to be based on the evaluation of infection/disease burden and health impact, the population health priorities as well as the available economic and human resources.

Information on the vaccine's safety and on the long-term epidemiological, economic and health consequences of population-based interventions over time represent important additional issues for policy makers [11]. While clinical studies supply results on vaccine safety and efficacy, mainly based on a short-term period, sources of long-term information are follow-up studies that are however, not always available. Nevertheless, mathematical models can prove to be useful alternative tools turning the results from short-term vaccine trials into predictors of long-term health outcomes [12].

A number of different types of mathematical models have been developed to foresee the long-term benefits and costs of vaccination [13-15]. Mathematical models could be a worthy tool to plan vaccination and alternative strategies (doses, boosters, immunization schedule, etc.) [16, 17]. The use of existing immunization data can represent the starting point from which to develop and apply a mathematical model to investigate the direct and indirect (herd immunity) effects of a vaccination program. Furthermore, probability models have been developed to predict the impact of different vaccines and to determine vaccination policies and the effects of different vaccine strategies, including hypothetical scenarios, can also be investigated. A realistic, age-structured, dynamic model can be developed, parameterized and fitted to epidemiological data. The individual-level (cumulative number of new infections prevented per 1000 vaccinated individuals) and population-level (cumulative percentage reduction in new infections) impact could be so predicted.

As new vaccines become available in the future, new recommendations for the vaccine's schedule and its proactive offer will be based on two main aims: the best resources allocation to maximize health outcomes (according equity principle) and the resource investment to guaranteed health rights (for vaccine preventable diseases) [18].

From a Public Health point of view, the epidemiological impact of the introduction a new vaccine in the population can be assessed by evaluating the incidence rate, mortality rate, permanent sequelae, complications and hospitalisations [19].

Economic evaluation and vaccines

New health technologies must be prioritized for correct policy decisions and economic data are needed to best allocate limited healthcare resources.

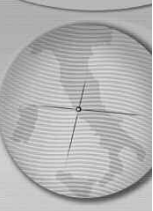
The main types of economic evaluation are the cost-benefit, the cost-effectiveness and the cost-utility analyses, which is a particular type of cost-effectiveness analysis [20]. Cost-effectiveness analysis determines which of the alternatives accomplishes a given objective at the lowest cost, where the effectiveness is expressed in terms of non-monetary units describing the desired objectives (life years, patients cured, etc.). With cost-benefit analysis comparisons are developed by reducing the costs and benefits of various alternatives to monetary terms. Cost-utility analysis allows a direct comparison of a wide range of medical interventions and is based on the quality-adjusted life year (QALY) or on the disability-adjusted life year (DALY). Vaccines are an important preventive measure world-wide and are socially useful interventions [21]. Their economic significance lies, partly, in the burden of disease that can be avoided and, partly, in the competition for resources between vaccines and other interventions [22].

Economic evaluation can be applied to prioritize research into vaccines [21], on the basis of both the reachable benefits in target population and the availability of good quality evidence.

From the Public Health point of view, vaccines warrant a cost-effectiveness approach, in order to determine if they are worthwhile, while just recommended vaccines might be more usefully assessed by either cost-effectiveness analyses or budget impact.

Economic evaluation of infectious diseases and attendant preventive interventions is complex because of the potential for "herd immunity" - the reduced opportunity for the infection to spread as there is a reduction in the opportunity for people to come in contact with infected individuals [23] and the need to consider indirect costs associated with vaccine development and infection/disease. For a full assessment of vaccination economic benefits, we should take into consideration the cost of the vaccine itself, possible vaccine wastage, the capital costs, the costs associated with possible adverse reactions as well as the costs of vaccine administration (current and capital costs) and educational campaigns.

Moreover a more accurate evaluation should consider the indirect costs of vaccination that are usually defined as the value of production lost to



society due to vaccination. These costs can be due to temporary absence from work, short and long-term disabilities and possible premature mortality [24]. Absenteeism from work, disabilities, disability program use, worker compensation program costs, worker turnover, family medical leave, and presenteeism account for an important part of economic burden [25].

Future economic evaluations have to be ensured as important decision tools to promote new vaccines; their relevance for decision makers may also be increased by addressing local budget constraints and vaccine price [26].

Since the continuous innovations of biotechnology production mechanism and the high cost of new products, governments need early clinical and economic data to manage the introduction and diffusion of a new product [27].

Vaccines economic evaluation integrates well into Evidence Based Vaccinology (EBV), which must be defined as the identification and the use of the best evidences to take decisions through all vaccines development and introduction phases [28]. Best evidence has to be searched for in the scientific literature or achieved by projecting and performing research on the different aspects and implications of a new vaccine's introduction. This corresponds with the aim of HTA.

Manufacturer's view, industry and research in vaccine development

There is evidence of the need for new cooperation amongst all stakeholders of immunization practices, including countries, industry, research institutions, foundations and international agencies such as the World Health Organization (WHO) and the United Nations Children Fund (UNICEF) to develop and introduce new vaccines, according to national priorities.

As regards to the manufacturers' view, it would guarantee the intellectual property protection, the improvement of research and the partnerships between industries and the public sector to promote the development of new therapies and to enhance access to both patented and generic medicines all over the world, especially in developing countries. Moreover, since, in 2002, vaccine spending accounted for only 1.7% of the total pharmaceutical market and UNICEF estimated that 34 million children, most of them in developing countries, were not reached by routine immunisation [29], financial resources would be provided to meet the goal of universal immunisation in developing countries over the 2004-2014 period. Financial resources are needed to purchase and introduce vaccines in the

developing countries, to reduce the time lag from their availability in industrialised countries and to stimulate researchers and manufacturers to study and develop the vaccines needed in developing world. This would be possible because of the new advanced technologies that have allowed manufactures to develop vaccines not thought to be possible before [30].

Since the need to change presentation and delivery of current vaccines [31], a HTA approach and the study of biotechnological and organizational aspects of new vaccines would be useful to investigate the best way to launch them.

Social and legal questions

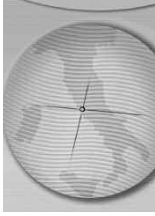
These items could be very different if one considers the setting where applying the vaccine procedure. We briefly describe these arguments considering both developed and developing countries separately.

Developed Countries

Vaccinations against life-threatening diseases are one of the greatest public health achievements in history [32]. Millions of premature deaths have been prevented, and countless more children have been saved from disfiguring illness.

Out of all of the branches of modern medicine, vaccinology can claim to be the one that has contributed most to the relief of human poverty and the spectacular increase in life expectancy in the last two centuries. It is the only scientific discipline that has eradicated an infectious disease - smallpox - responsible for 8-20% of all deaths in several European Countries in the 18th century. Currently, it is estimated that immunization saves the lives of 3 million children a year but 2 million more lives could be saved by existing vaccines. The success of vaccines in controlling and eliminating diseases has, paradoxically, been the cause of a revival of the anti-vaccination movement which in the absence, in developed countries, of many erstwhile common infectious diseases such as diphtheria, tetanus, polio, pertussis, measles, rubella and mumps has come to believe that vaccination is not only no longer necessary but is even dangerous [33]. This is because it accepts, as "reactions", any untoward health event that occurs after the administration of a vaccine.

Vaccinations have been and are a most successful instrument of preventive medicine. Today, however, vaccines are becoming a victim of their success - many individuals have never witnessed the debilitating diseases that vaccines protect against, allowing complacency toward immunization



requirements to build. Anti-vaccination sentiment is growing fast in the United States, in large part due to the controversial and hotly disputed link between immunizations and vaccines safety and efficacy, but also for religious and philosophical purposes [34, 35].

After the development of a vaccine, some legal questions arise. Since field trials should be performed in those age groups which shall be protected - can children give "informed consent"? Should the vaccination be compulsory or should it be recommended by public health authorities? Should there be compensation for injuries related to immunisation? The possibility to develop new vaccines and the readiness of the population to cooperate in vaccination campaigns depends very much on a clear solution of these questions.

The parent's belief regarding compulsory vaccination for school entry is significantly associated with beliefs in the safety and utility of vaccines, as well as intention to have the youngest child fully vaccinated.

Movements to introduce broad "philosophical/personal beliefs" exemptions administered without adequate public health oversight threaten this success. Health professionals and child welfare advocates must address these developments in order to maintain the effectiveness of the nation's mandatory school vaccination programs.

The most common reason stated for requesting exemptions was concern that the vaccines might cause harm. Parents of exempt children were significantly more likely than parents of vaccinated children to report low perceived vaccine safety and efficacy, a low level of trust in the government, and low perceived susceptibility to and severity of vaccine-preventable diseases. Parents of exempt children were significantly less likely to report confidence in medical, public health, and government sources for vaccine information and were more likely to report confidence in alternative medicine professionals than parents of vaccinated children [36]. Residence in a state that permits philosophical exemption to vaccination was also significantly associated with a parent's opposition to compulsory vaccination for school entry.

Providing basic information to parents regarding vaccines and vaccine-preventable diseases may help to reduce opposition to compulsory vaccination by reinforcing the safety and importance of routine childhood vaccinations [37].

Continued efforts must be made to educate parents about the utility and safety of vaccines, especially parents requesting non medical exemptions to school immunization requirements.

The experience in the United States with the vaccine liability crisis demonstrates the vulnerability of public health policy and practice standards to independent developments in the legal arena. Scientific progress in the fields of immunology and molecular biology offer promise for the control of an increasing number of communicable diseases through immunization.

Legal protection for pharmaceutical laboratories, manufacturers, and providers are appropriate incentives to the continued development, supply, and administration of effective, affordable vaccines. At the same time, potential recourse to litigation in the courts in the event of vaccine-related injury provides society with desirable assurances of enforceable industrial and professional standards, as well as financial support for those who sustain serious adverse reactions to licensed vaccines.

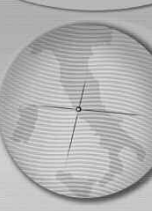
Other developments that in the last two decades have hampered vaccine usage have been the exploding costs of research, development and manufacture of new vaccines and the emphasis still placed on therapy in preference to prevention in medicine. This has led to the erroneous perception that vaccines are expensive although they are, in most cases, more cost-effective than the popular wait-see-treat approach.

Developing Countries

On the other hand, in developing countries, where economic development is lacking and literacy rates are low, priority must be given to primary health care and to the establishment of sustainable health care delivery systems.

In these countries infectious diseases are the main cause of mortality and morbidity. Although childhood immunizations have proved to be one of the most effective means of preventing and controlling the spread of infectious and communicable diseases, thousands of preschool children, particularly children from urban African American poor families, are not being immunized [38]. Immunization of preschool children is a function of the interrelationship among health-seeking behaviour of parents, financial and non financial barriers to health care, and provider practices that inhibit appropriate immunization. Two problems that confront the delivery of health services, including immunization, are lack of funds and lack of access to susceptible populations. Approaches to the lack of funds problem include fee for service, taxation, better management of existing resources, reallocation of health resources, and increased funding from donor nations.

Improving access to existing public programs, facilitating community organization efforts,



assisting communities through self-help and mutual-aid initiatives, and supporting national efforts can improve immunization status among poor children [37].

Bioethical issues and vaccines

There are many ethical problems in HTA and we can't imagine the future of HTA without thorough ethical evaluations. Vaccines can be included among the arguments for discussion along with any other HTA aspect. Important ethical considerations for vaccines concerns two preliminary questions: 1. is an obligation to vaccinate the entire population ethically admissible? 2. Can this fundamental prevention activity be entrusted to the voluntary adhesion of the population? It's well known that the fundamental goal of vaccination policies is to reach the largest number of citizens, in order to improve the population's health status by the prevention of infectious diseases. The ethical approach in vaccination aims to evaluate the social legitimisation of medical actions for an intervention that could on one hand produce adverse effects for single individuals while on the other hand could produce important gains in saving human lives, improve quality of life and obtaining economical advantages.

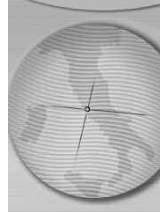
The utilitarian bioethics approach can provide interesting answers to these ethics dilemmas. Utilitarian bioethics is a very controversial branch of Utilitarian ethics that encourage the utilisation of medical resources where they will contribute most to the sum of the number of happy people in the community. Ethical suggestion by utilitarianism can provide an interesting point of view regarding this topic. The utilitarian ethics, formulated first by Jeremy Bentham in 1781, and later elaborated by the philosopher John Stuart Mill, states that the rightness of an action entirely depends on the value of its consequences, and that the usefulness can be rationally estimated. The utilitarian bioethical thought seems to be useful in the ethical vaccination debate. Utilitarianism bioethical philosophers direct their arguments in a simple direction: to make the number enjoying a good health condition as great as possible [39]. Utilitarian methods met many difficulties in resolving economic macroallocation problems in health care [40] but it seems to be able to give a valid orientation in the ethical evaluation of vaccinations.

This intervention has a particular relief in the public health approach, that considers public interest as pre-eminent in comparison to individual risks and problems. So, for many years,

and still in some countries, vaccinations are obliged by law. This approach is not easy but is necessary. Public Health has in fact the moral obligation to organize public systems to obtain a widely extended vaccination of the most part of the population. The aim is to reach a high enough level of vaccine protection to prevent and, if feasible, eradicate the infectious disease.

Italian Law has well considered the ethical utilitarian approach, by interesting sentences, as well as n. 307 / 1990, in which the Supreme Court affirms that if a treatment is finalized not only to improve or defend the health condition of a single citizen but also to defend the health condition of the other citizens is an interest of the community, the vaccine obligation is not incompatible with the Italian Constitution. In the specific field of the polio vaccine the sentence 118/96 considers that the law can deliberately do an evaluation of the collective and individual affairs reaching the limit of those that are been denominated "juridical tragic choices". These are the choices that a society retains to make in order to obtain a good that involves the risk of an evil (serious although rare adverse effects).

But the best way for the future is firmly linked with overcoming the need for obliged vaccinations. The free informed choice of citizens needs expanding upon with regards to another typical bioethical topic: informed consent based upon correct information about direct and indirect risks of illness towards which the vaccination is recommended; benefits of the vaccination; risks of the vaccinations and possible alternatives to these practice. For these difficult problems, an important point of reference is the University of Pennsylvania Center for Bioethics, which founded the Ethics of Vaccines Project [41]. The Project is based on the consideration that notwithstanding the fact that vaccines have reduced or eradicated infectious disease all over the world, and vaccines is one of the safest and most effective preventative options available to the public in Public Health, many ethical issues involved in the vaccines have never been systematically studied in a practical framework for action. Ethics could help and guide researchers, pharmaceutical companies, public health agencies, health care providers and citizens to consider vaccines policies in their real dimension: safe, effective and ethical intervention to improve Public Health. The Project aims to develop an ethical framework to help this area of public-health. As suggested by Arthur Caplan, Director of Penn's Center for Bioethics, the great interest for vaccines enforces the ethic evaluation: "Just as Hurricane Katrina uncovered a number of



very unacceptable realities associated with our nation's preparedness and our response to the poorest of our citizens, the prospect of an avian flu pandemic - and it is still a prospect - is bringing into sharp focus where we need to prioritize our energies in terms of the ethics around the role of vaccine in global public health".

An example of HTA report project

Very recently a joint project promoted by the Institute of Hygiene, Catholic University of the Sacred Heart, and by the company Glaxo-Smith-Kline has started in order to produce a HTA report on the vaccine against the Human Papillomavirus (HPV). The choice on this vaccine was done, taking into account the fact that this is a new vaccine and potentially could have a great impact on people's health, in particular for women. The project is ongoing and a specific action plan was developed in order to consider all the aspects that will influence the decision makers' choice. The following steps are to be considered in our project:

- the evaluation of the epidemiology of the disease in Italy, through the interrogation of data banks and the scientific literature;
- the systematic review of studies in relation to the impact of the HPV vaccination on the epidemiology of HPV related diseases. We will review both studies that consider empirical data from the pre-vaccination and post-vaccination eras and mathematical modelling of the disease's course;
- the evaluation of the use of health care services by those suffering from cervical cancer, through the consultation of hospital discharge records;
- an in-depth survey of the 'willingness to pay' of those suffering from cervical cancer, in order to assess peoples preparedness to pay for treatment in order to avoid the development of the disease;
- a systematic review of the vaccine's clinical trials, and, if possible, a meta-analysis of the effectiveness and safety studies, applying the most modern criteria of RCT quality assessment;
- mathematical modelling of the incidence reduction of HPV infections within 10-15 years, taking into consideration the estimated aging of the Italian population;
- an economic evaluation of the impact of the vaccination, using a cost-effectiveness analysis expressing the final results in terms of quality-adjusted life years gained (QALYs);
- an evaluation of the impact of the vaccination programme on the health system (the relationship between Industry and the Government; the surveillance system of those vaccinated);

- an evaluation of organizational aspects of the vaccine's introduction, analysing, in particular, the relationship between the different decisional levels (national, regional);
- an analysis of the ethical, social (acceptability; availability; accessibility, information) and legislative aspects of vaccination.

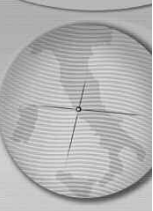
Conclusions

We proposed a HTA approach for considering the new introduction of a vaccine that potentially could have a great impact on the population health.

A HTA report on the new vaccine could represent a new important tool to support the choice of decision makers in order to better inform the allocation of economic resources and maximize healthcare services, since it takes into account not only the burden and the epidemiology of the disease, and the economic evaluation of different scenario, but also the social, legal and bioethical aspects. For HTA to support the introduction of new technologies, and new vaccines can be considered in this sense, there is the need to use a process that is well defined, transparent and widely used.

References

- 1) Kieny MP, Excler JL, Girard M. Research and development of new vaccines against infectious diseases. *Am J Public Health* 2004;94(11):1931-5.
- 2) Kieny MP, Girard MP. Human vaccine research and development: An overview. *Vaccine* 2005;23(50):5705-7.
- 3) Andre FE. How the research-based industry approaches vaccine development and establishes priorities. *Dev Biol (Basel)* 2002;110:25 - 9.
- 4) WHO, UNICEF, GIVS. Global Immunization Vision and Strategy 2006-2015. Available from: http://www.who.int/vaccines-documents/DocsPDF05/GIVS_Final_EN.pdf [Accessed March 22, 2007].
- 5) Drummond M. Economic appraisal of health technology in the European Community. Oxford: Oxford University Press, 1987.
- 6) Warren K, Mosteller F. Doing more good than harm: the evaluation of health care interventions. New York: New York Academy of Sciences, 1993.
- 7) US Congress, House of Representatives, Committee on Science and Astronautics. Technology assessment. Statement of Emilio Q. Daddario, chair, Subcommittee on Science, Research and Development. Washington: 90th Congress, 1st session; 1967:9-13.
- 8) Banta D, Battista R, Gelband H, Jonsson E. Health care technology and its assessment in eight countries. Washington, DC: United States Congress, 1995.
- 9) Battista RN, Hodge Mj. The evolving paradigm of health technology assessment: reflections for the millennium. *CMAJ* 1999;160 (10):1464-7.
- 10) Banta D. The development of health technology assessment. *Health Policy* 2003; 63(2):121-32.
- 11) Garnett GP, Dubin G, Slaoui M, Darcis T. The potential epidemiological impact of a genital herpes vaccine for women. *Sex Transm Infect* 2004;80(1):24-9.
- 12) Weinstein MC, Toy EL, Sandberg EA et al. Modeling for health care and other policy decisions: uses, roles, and validity. *Value Health* 2001;4(5):348-61.
- 13) Bos JM, Rumke H, Welte R, Postma MJ. Epidemiologic



- impact and cost-effectiveness of universal infant vaccination with a 7-valent conjugated pneumococcal vaccine in the Netherlands. *Clin Ther* 2003;25(10):2614-30.
- 14) Schwartz EJ, Blower S. Predicting the potential individual- and population-level effects of imperfect herpes simplex virus type 2 vaccines. *J Infect Dis* 2005;191(10):1734-46.
- 15) Trotter CL, Gay NJ, Edmunds WJ. Dynamic models of meningococcal carriage, disease, and the impact of serogroup C conjugate vaccination. *Am J Epidemiol* 2005;162(1):89-100.
- 16) Byrnes GB. A Markov model for sample size calculation and inference in vaccine cost-effectiveness studies. *Stat Med* 2002;21(21):3249-60.
- 17) Lietman T, Blower SM. Potential impact of tuberculosis vaccines as epidemic control agents. *Clin Infect Dis* 2000;30(Suppl 3):S316-22.
- 18) Moree M, Ewart S. Policy challenges in malaria vaccine introduction. *Am J Trop Med Hyg*. 2004; 71(2 Suppl):248-52.
- 19) Piano Nazionale Vaccini 2005-2007. Available from: http://www.ministerosalute.it/imgs/C_17_normativa_526_ult_erioriallegati_ulteriorereallegato_0_alleg.pdf [Accessed March 22, 2007].
- 20) Szucs T. Cost-benefits of vaccination programmes. *Vaccine* 2000;18(Suppl 1):S49-51.
- 21) Jefferson T. Do vaccines make best use of available resources? (in other words are they cost-effective?). *Vaccine* 1999;17(Suppl 3):S69-73.
- 22) Szucs TD. Health economic research on vaccinations and immunisation practices - an introductory primer. *Vaccine* 2005;23 (17-18):2095 - 103.
- 23) John TJ, Samuel R. Herd immunity and herd effect: new insights and definitions. *Eur J Epidemiol* 2000;16(7):601-6.
- 24) Grover SA, Ho V, Lavoie F, Coupal L, Zowall H, Pilote L. The Importance of Indirect Costs in Primary Cardiovascular Disease Prevention. *Arch Intern Med* 2003;163(3):333-9.
- 25) Goetzel RZ, Hawkins K, Ozminkowski RJ, Wang S. The health and productivity cost burden of the "top 10" physical and mental health conditions affecting six large U.S. employers in 1999. *J Occup Environ Med*. 2003;45:5-14.
- 26) Brinsmead R, Hill S, Walker D. Are economic evaluations of vaccines useful to decision-makers? Case study of Haemophilus influenzae type b vaccines. *Pediatr Infect Dis J* 2004;23(1):32-7.
- 27) Mason J. Challenges to the economic evaluation of new biotechnological interventions in healthcare. *Pharmacoeconomics* 1999;16(2):119-25.
- 28) Nalin DR. Evidence based vaccinology. *Vaccine* 2002;20(11-12):1624-30.
- 29) Peny JM, Gleizes O, Covillard JP. Financial requirements of immunisation programmes in developing countries: a 2004 - 2014 perspective. *Vaccine* 2005;23(37):4610 - 8.
- 30) Coleman MS, Sangruee N, Zhou F, Chu S. Factors Affecting U.S. Manufacturers' Decisions To Produce Vaccines. *Health Aff (Millwood)* 2005;24(3):635-42.
- 31) Clements CJ, Wesselingh SL. Vaccine presentations and delivery technologies - what does the future hold? *Expert Rev Vaccines* 2005;4(3):281-7.
- 32) Andre FE. Vaccinology: past achievements, present roadblocks and future promises. *Vaccine* 2003;21(7-8):593-5.
- 33) Feikin DR, Lezotte DC, Hamman RF, Salmon DA, Chen RT, Hoffman RE. Individual and community risks of measles and pertussis associated with personal exemptions to immunization. *JAMA* 2000;284(24):3145-50.
- 34) Salmon DA, Haber M, Gangarosa EJ, Phillips L, Smith NJ, Chen RT. Health consequences of religious and philosophical exemptions from immunization laws: individual and societal risk of measles. *JAMA* 1999;282(1):47-53.
- 35) Kennedy AM, Brown CJ, Gust DA. Vaccine beliefs of parents who oppose compulsory vaccination. *Public Health Rep* 2005;120(3):252-8.
- 36) Salmon DA, Moulton LH, Omer SB, DeHart MP, Stokley S, Halsey NA. Factors associated with refusal of childhood vaccines among parents of school-aged children: a case-control study. *Arch Pediatr Adolesc Med* 2005;159(5):470-6.
- 37) Briss PA, Rodewald LE, Hinman AR, et al. Reviews of evidence regarding interventions to improve vaccination coverage in children, adolescents, and adults. The Task Force on Community Preventive Services. *Am J Prev Med* 2000;18(1 Suppl):97-140.
- 38) Arya SC. Human immunization in developing countries: practical and theoretical problems and prospects. *Vaccine* 1994;12(15):1423-35.
- 39) Sidgwick H. Methods of Ethics. Available from <http://www.la.utexas.edu/methsidg/me/index.html> [Accessed March 22, 2007].
- 40) Bucci R. *Etica e mercato nella sanità*. [Ethics and market in health care]. Roma: Esiesse, 1995.
- 41) University of Pennsylvania Center for Bioethics. Ethics of Vaccines Project. Available from: www.bioethics.upenn.edu/vaccines [Accessed March 22, 2007].