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The public health evaluation of vaccines

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Vaccines represent some of the most important tools available for the prevention of diseases. In addition to protecting the vaccinated individual from developing a potentially serious disease, they help protect the community by reducing the spread of infectious agents. Therefore, there are not only benefits for the single individual, but also advantages for the entire community and the society. This very simple consideration makes unique the public health evaluation of vaccines, with substantial differences with other public health interventions and a need to adopt different criteria to develop recommendations for use.

The public health evaluation of vaccines is challenged by several factors. Vaccine randomized trials often lack adequate sample size, fail to provide critical study details, exclude important populations, and rely on proxies for important outcomes. Observational studies are necessary to complement randomized studies in evaluating the effectiveness of vaccines in routine use and to monitor adverse effects of vaccine. In the past recommendations for use of a vaccine depended on the balance of benefits of vaccination, risks of disease, and risks of vaccination. Now the continuing development of new vaccines raises ethical issues related to the fact that it is not self-evident that all available and affordable vaccines should be incorporated into national or international vaccination programmes. What principles should be applied in deciding what counts as an adequate programme? Where choices have to be made about priorities in this area, how should they be made? Since vaccines are usually made by pharmaceutical companies, a transparent cooperation between researchers, public health practitioners and the vaccine industry is essential.

The workshop organized by the EUPHA Section on Public Health Epidemiology at the Annual Conference of the European Public Health Association in Lisbon in November 2008 addressed most of these issues, providing insights on how evaluation of vaccines efficacy, effectiveness and safety should be performed and giving the possibility to public health epidemiologists in Europe to make some reflections about the role of epidemiology in this field [1]. There were three presentations. The first presentation was made by Pierluigi Lopalco of ECDC and was an overview on methods to perform the evaluation of vaccines and vaccination strategies, outlining differences between the evaluation of vaccines and immunization programs. The second presentation of Hans Houweling of the Health Council of the Netherlands focused on the general criteria to include vaccinations into a national vaccination program, describing the Dutch experience. The last presentation was given by Mark Fletcher on behalf of the European Vaccine Manufacturers (EVM) and expressed the point of view of industry, outlining how harmonization of vaccination schedules across Europe might facilitate vaccine development.

The role of epidemiology in the development of a vaccination program, at least at the theoretical level, is well established. Before licensing a vaccine, its safety and efficacy must be established, using controlled clinical trials. Post-licensing evaluation is of equal importance, however, not only to monitor the impact of the

vaccination program on the target diseases but also to identify changes in vaccine efficacy under field, compared to study conditions, and to detect rare or new adverse events that may not have been apparent during the initial clinical trials. In this issue of the journal, Lopalco reviews the different methods that are available to evaluate both safety and efficacy in the field, highlighting the need to perform a careful assessment not only of the vaccines, but also of the vaccination programmes [2]. The value of serosurveys in the evaluation of vaccination programmes is evident from the paper of Langiano et al., who analyzed the prevalence of rubella immunization in the province of Frosinone (Italy) [3]. Fletcher describes the use of some of the paediatric combination vaccines in different European countries, emphasizing that the evaluation of the existing vaccines, as well as the introduction of the new ones, is complicated by discordant infant vaccination schedules across the EU [4].

The production of guidelines and evidence-based recommendations on the use of vaccines is abundant. The World Health Organization (WHO) publishes a series of regularly updated position papers concerning primarily with the use of vaccines in large-scale immunization programs and designed for use mainly by national public health officials and immunization program managers. The Canadian Task Force on Preventive Health Care (CTFPHC) and the Advisory Committee on Immunization Practice (ACIP) in the U.S. develop and regularly update written recommendations for the routine administration of vaccines to children and adults.

In Europe, the European Center for Disease Prevention and Control (ECDC) takes a strong interest in vaccines and vaccine preventable diseases and provides Member States with scientific support to plan and implement correct immunization strategies. The ECDC works closely with other European networks on vaccine preventable diseases, including those financed by DG Sanco (VENICE, VACSATC, etc.), as well as with the experts in the field of the different Member States. Nevertheless, immunization policy remains largely a Member State competence and it is decided generally following the advice of national public health governmental agencies or associated advisory groups. As it may be expected, political considerations are an important element of the decision making process concerning vaccinations at Member States level.

In the vaccine field providing an evidence-based approach universally accepted is difficult, as the relevant information reflects factors which may have certain degrees of uncertainty and depends on different value judgements. ECDC has identified some key elements of the decision making process concerning the inclusion/exclusion of a vaccination into a national immunization program: seriousness and extent of disease burden, effectiveness of the vaccination and alternative measures, costs and public health organization, while political considerations is not an important element at the ECDC level. There is a need to integrate different forms of evidence (expert analysis, country data on incidence of diseases and vaccination schedules and coverages, sero-surveys, observational studies, experimental studies, systematic reviews and meta-analysis, economic evaluations), and sometimes these different forms of evidence show a certain degree of disagreement.

The case of influenza vaccination is emblematic. All guidelines recommend the use of influenza vaccination in the elderly. The Resolution 56.19 (28 May 2003) of the World Health Assembly urges Member States to increase "vaccination coverage of the elderly population of at least 50% by 2006 and 75% by 2010", and the WHO coverage rate objectives are fully supported by the European Parliament within the strategy against an influenza pandemic. Three meta-analyses were published on the efficacy and the effectiveness of influenza vaccination in the elderly [5-7]. While the first two are highly supportive for the use of vaccination in the elderly, the third one states that "according to the

reliable evidence, the usefulness of influenza vaccines for the elderly living in the community is modest". This meta-analysis is likely to have a negative impact on vaccination rates in Europe.

Also the use of influenza vaccination in healthy children is controversial. While APIC recommends routine influenza immunization for healthy children, this vaccination is not recommended in Europe. Three meta-analyses were performed to assess the efficacy and the effectiveness of influenza vaccination in healthy children [8-10], with quite contrasting conclusions. Although published meta-analyses currently receive more citations that any other types of study design [11], there is some evidence that a number of meta-analyses in vaccinology show some methodological deficiencies [12]. However, meta-analysis is a valuable tool in vaccinology, and the application of the new advanced techniques (multiple-treatments meta-analysis) may help to solve very important practical issues, such as, for example, the optimal dose of the H5N1 vaccine [13].

One way to advance on these issues is to see whether we can agree a set of suitable guiding principles to be used to formulate coherent and ethically justified collective vaccination programmes. The resulting norms could play a similar role to that of Wilson and Jungner's well-known principles for screening programmes [14]. Recently the Health Council of The Netherlands has developed seven criteria for the inclusion of vaccinations in the National Immunization Programmes [15]. These seven criteria, grouped under five thematic headings, are

Table 1. The seven criteria developed by the Health Council of the Netherland for the inclusion of vaccinations in the National Immunization Programme (15).

Seriousness and extent of the disease burden

1. The infectious disease causes considerable disease burden within the population
   - The infectious disease is serious for individuals, and:
   - The infectious disease affects or has the potential to affect a large number of people.

Effectiveness of the vaccination

2. Vaccination may be expected to considerably reduce the disease burden within the population.
   - The vaccine is effective for the prevention of disease or the reduction of symptoms.
   - The necessary vaccination rate is attainable (if eradication or the creation of herd immunity is sought).
3. Any adverse reactions associated with vaccination are not sufficient to substantially diminish the public health benefit.

Acceptability of the vaccination

4. The inconvenience or discomfort that an individual may be expected to experience *in connection with his/her personal vaccination* is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.
5. The inconvenience or discomfort that an individual may be expected to experience *in connection with the vaccination programme as a whole* is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.

Efficiency of the vaccination

6. The ratio between the cost of vaccination and the associated health benefit compares favourably to the cost-benefit ratio associated with other means of reducing the relevant disease burden.

Priority of the vaccination

7. The provision of vaccination may be expected to serve an urgent or potentially urgent public health need.

outlined in Table 1. The criteria are based on two ethical principles: i) that the best possible protection should be afforded to the population as a whole and ii) that benefit should be fairly distributed across population groups, with protection provided on the basis of need.

The seven principles do not offer clear-cut answers to all ethical and scientific disputes concerning vaccination. Their function is to promote and guide reflection about the development, adjustment and implementation of coherent and ethically justified policies for collective vaccination and their application requires the thorough analysis of scientific data and considerable skills. The Health Technology Assessment (HTA) approach, described by La Torre in this issue of the Journal [16], has been developed in some European countries to examine in a multidisciplinary way the clinical, economic, organizational, ethical, juridical, social and cultural implications of the introduction or the implementation of a specific technology. Although it has been named as "an old bottle with a new brand" since it encompasses different but well known tools (epidemiological evaluation, economic appraisal, etc.), there is no doubt that the HTA approach is able to address most of the seven criteria and could be considered a very valuable tool for the public health evaluation of vaccines.

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