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Lifelong vaccination as a key disease-prevention strategy

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Abstract

Vaccination is traditionally considered as a measure addressed to infants and children. Indeed, in natural conditions, vaccine-preventable infections are mainly spread at a young age. The implementation of routine and mass vaccination programmes has led to the eradication of smallpox and to the elimination of poliomyelitis in many regions of the world, together with the control of once life-threatening diseases like diphtheria and tetanus. In more recent times, the development of new generation vaccines and the changing epidemiological profile of many vaccine-preventable diseases have greatly changed the objectives and the target of today's immunization strategies. The objective of this article is to highlight and discuss the evolution of vaccination strategies from measures aimed at protecting children to a practice that is needed throughout life. Adolescents and adults need immunization for several reasons: they may not have received the vaccines usually administered in childhood; new vaccines tailored for adolescents and adults have become available; immunity acquired thanks to immunization in childhood can fade; and older adults or those who are chronically ill are more susceptible to vaccine-preventable diseases and to their complications. The changing demographic profile of both industrialized countries and of countries in transition towards an 'aging' population, and the shift of several infectious diseases towards adulthood make it imperative that new infrastructures to deliver vaccines and new investments in immunization are investigated. Such a change of perspective is needed both to preserve health and to guarantee the sustainability of health systems.

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Background

Vaccination is traditionally considered as a measure that is addressed to infants and children. In natural conditions, vaccine-preventable infections are mainly spread at a young age. The start of attendance at day-care centres, nurseries and primary schools is usually the typical age of acquisition of highly contagious infections transmitted directly or indirectly through airborne droplets or by the faecal–oral route.

The implementation of routine and mass vaccination programmes has led to the eradication of smallpox and to the elimination of poliomyelitis in many regions of the world, together with the control of once life-threatening diseases like diphtheria and tetanus.

In the last three decades, the development of new technologies (like recombinant DNA and conjugation of polysaccharides) to produce vaccines that were impossible to obtain using the conventional cultural techniques, has allowed the introduction of immunization programmes against hepatitis B, *Haemophilus influenzae* b, and pneumococcal and meningococcal diseases in many countries of the world. The efforts of countries and international agencies to increase vaccination coverage have produced notable results [1]. In some cases, the positive effects on mortality are not limited to the vaccine-preventable disease itself, but expand to fatalities caused by other agents whose pathogenic effects, in natural conditions, are increased by the vaccine-preventable infectious disease. For instance, a 13% increase of global coverage against measles obtained between 2000 and 2010 has translated into a

*c.*74% reduction of measles mortality [2] and an indirect effect on casualties due to pneumonia and diarrhoeal diseases.

In more recent times, the development of the latest generation of vaccines and the new epidemiological profile of many vaccine-preventable diseases have greatly changed the objectives and the target of today's immunization strategies.

For instance, the availability of human papillomavirus (HPV) vaccines prompted health authorities to plan and organize universal immunization programmes aimed at a non-traditional target for previous vaccination strategies, that of adolescents.

We also have innovative tools, like new pneumococcal and herpes zoster vaccines, that we can use to preserve health and quality of life in the elderly population, an increasingly numerous target where preventive activities can substantially contribute to the sustainability of healthcare systems.

On the other hand, the most affected age groups for traditional vaccine-preventable diseases (i.e. measles) have changed because of suboptimal coverage in children. Measles has become mainly a disease of adolescents and adults in many industrialized countries.

The objective of this article is to highlight and discuss the evolution of vaccination strategies from measures aimed at protecting children to a practice that is needed throughout life.

Priority Setting on Vaccination Programmes and New Ways to Measure Immunization Impact

In the past, the drivers behind the decision to introduce a vaccination programme were mainly the number of deaths and serious disease cases. Relatively few vaccines were available, and pharmaco-economic evaluations were not needed, because the advantage of vaccination was self-evident and there was a preference for vaccination early in life. Parents accepted vaccination almost invariably, and the costs connected with vaccination programmes were low.

Since the beginning of the 21st century, the world of vaccination has started to change: many new vaccines are in line and the approach to their introduction is focused on evidence-based prevention. However, the communication landscape has changed dramatically, and, as a consequence of the reduction of incidence of once threatening diseases thanks to widespread vaccination, parents are more concerned by the adverse reactions of vaccines than by the disease itself. Vaccines have a higher technological content and higher costs, at least in the first years following their availability.

Also, the concept of vaccine-preventable diseases has changed. Traditionally, the effect of vaccination was measured as the reduction (usually in the short term) of deaths, serious sequelae, complications and number of cases for well-characterized acute diseases. Measurement of effects is performed using standard surveillance methods (incidence, hospitalizations, mortality rates, etc.), and the end objective of vaccination programmes is frequently elimination or even eradication of an infectious agent.

With the newly developed vaccines, the impact of vaccination strategies is less frequently only a direct effect, it is often prolonged (vaccines like HPV, for instance, extend their effects for many decades to come), and it is not only 'medical' and not easily measurable, given the frequent impact on economics, on social settings or quality of life [3]. As a consequence, methods to measure the effects of an immunization programme need to be adapted to the new scenario. For instance, for influenza, the reduction of hospitalizations and of work absenteeism might be more relevant than the simple decrease of disease cases; for rotavirus diarrhoea, the impact on family disruption is among the most relevant expected outcomes; for herpes zoster, vaccination is expected to impact especially on quality of life and on social disruption. In addition, there is a need for surrogates of protection when the maximum expected benefit is delayed (as for HPV). In brief, we need to shift from the concept of prevention of disease to that of prevention of illness (also including consequences on social disruption, resource use, protection of high-risk groups, family and community members, and impact on work absenteeism).

The characteristics of our evaluation tools are also changing: for surveillance purposes, it is advisable to introduce and validate the most modern tests for the surveillance of infections (nucleic acids testing, genotyping, sequencing, etc.).

On the other hand, a complete evaluation of the most relevant aspects of the introduction of a new vaccine (from an epidemiological, economic, ethical, organizational and communicational point of view) is needed today and is included in the broad concept of Health Technology Assessment (HTA) [4]. In this new landscape, it is necessary to implement the evaluation techniques of evidence-based prevention, not only through meta-analysis and systematic revision of efficacy and safety of vaccines, but also by expanding a multidisciplinary approach (together with mathematicians, demographists and economists) to develop dynamic models on the epidemiology of disease and on the impact of new vaccination strategies. Since HTA also includes considerations of acceptability and ethical and economic issues, we need to explore new methods for the surveillance of social wellness, quality of life and impact on productivity. Last but not least, in a scenario of more attention given to adverse events following vaccination than to the diseases prevented by vaccines, we need to learn and experience relevant communication skills.

Vaccination at Adolescent Age

Adolescence is a period of life when vaccination is of special importance, because of different and partly overlapping factors: a continuing risk of disease (for instance, meningococcal meningitis, tetanus), with a possible need for booster doses; an epidemiological shift of disease incidence because of incomplete immunization programmes in childhood (i.e. measles and rubella); the forthcoming risk for some infections, due to the beginning of sexual life or at-risk behaviours (smoking, drug abuse) (for instance, HPV and hepatitis B). Moreover, adolescence is also a sort of 'filter age' to verify immunity to infections that might have a more serious outcome when contracted in adulthood (like varicella, hepatitis A and again measles and rubella).

The difficulty of reaching adolescents with an effective vaccination offer lies mainly on the typical features of subjects in this age group: increase of independence, risk behaviour and concrete thinking, and decrease (or absence) of parental influence, health worries and orientation to the future. In addition, organizational issues (who is responsible and where vaccines should be delivered) can be important [5].

Vaccination of Adults: the New Frontier

Vaccine-preventable infectious diseases have decreased in childhood, but have increased their relative and absolute importance in adulthood.

Today, adults need vaccinations for different reasons. (1) They may not have received vaccines usually administered in childhood. Vaccines have been progressively inserted into the routine vaccination schedule, and high coverage is sometimes not achieved for relatively long periods. For this reason, present day adults may still be unprotected, for instance, against tetanus, measles, rubella and other vaccine-preventable infections. (2) New vaccines tailored for adults have become available. For instance, the herpes zoster vaccine is specifically designed to protect adults and the elderly against the most dreadful consequence of shingles, i.e. post-herpetic neuralgia. (3) Immunity acquired thanks to immunization in childhood can fade. A typical example is represented by pertussis, which induces a non-permanent immunity both after natural infection and after vaccination, for which reason, periodical booster doses are needed to maintain protection. (4) Older adults or those who are chronically ill are more susceptible to vaccine-preventable diseases and to their complications. It is particularly important to prevent influenza and pneumococcal infections in subjects who might experience very serious consequences and even fatalities as a result of their condition of old age or already existing serious chronic diseases.

The demographics of industrialized countries, and of countries in transition, explains an increasingly important susceptibility to infectious diseases that particularly affects the elderly. As a matter of fact, it is foreseen that in 2050, in several European countries (for instance, Italy) the proportion of the elderly (>65 years) will be about one-third of the total population [6]. This means that a longer life expectation is coupled with a progressive increase in the number of subjects with an impairment of the immune system, which in turn translates into an exponential increase of susceptibility to diseases like pneumonia and herpes zoster.

However, not only are numbers of elderly in the population changing. Also, the typical social profile of today's older adults is different from yesterday's. In the past, adults worked hard until retirement, when their only remaining purpose was to raise new generations, helping children to perform their duties, and travelling only exceptionally. Care of older infirm adults was handled at home by relatives.

Today, we have an increasing number of people who remain active until advanced age, who do more sports, travel very frequently, live independently from new generations, and demand more health services (including vaccinations able to protect them and preserve their good health). However, in contrast, the number of institutionalized elderly people is also increasing, and the environment of such institutions may increase the chances of transmission of certain diseases like influenza and pneumococcal pneumonia.

Risk-based and Aged-based Recommendations

It is also worth noting that at least 80% of those aged >65 years suffer from a condition of chronic illness that indicates the need for the administration of certain vaccines (i.e. influenza, pneumococcus). However, although there are commendable exceptions, risk-based approaches to vaccine administration usually fail (as demonstrated by experiences of hepatitis A, hepatitis B, influenza) [7]. The reason for such failures lies in the need to identify subjects with specific diseases, that are often followed up by specialists rather than by their general practitioners. Specialists should be fully informed on vaccine characteristics and indications (which very rarely occurs), and a clear decision on who should be responsible for immunizing and registering vaccination should be taken, which is again a hard-to-reach result. Age-based vaccination strategies are not the solution to all problems, but can substantially help to increase coverage in those above a

certain age threshold. They allow easy access to the target group, irrespective of the specific clinical condition, through an infrastructure that either exists, or is easily constructible. A possible added value of age-based vaccination strategies is the opportunity to obtain a herd protection effect due to high coverage in closed settings (such as, for instance, residential homes for institutionalized patients), which would not be possible with a risk-based-only strategy.

From a public health point of view, it is therefore more feasible and less time- and resource-consuming to lower the threshold age for active offer of certain vaccines, rather than trying to find each subject at risk selectively—a suggestive comparison has been made with fishing using a net rather than a fishing rod (M. Faccini, personal communication). Which, of course, does not mean that we are allowed to stop our efforts to reach every subject at risk of any age with recommended vaccinations.

The recognition of the added value in terms of higher coverage that can be reached in at-risk subjects, and the evidence of indirect effects of mass vaccination on those who suffer the worst consequences of the disease, are the reasons for the progressive extension of influenza vaccination recommendation in the USA, from the initial lowering to a population >50 years, to the present day recommendation of use at all ages (since 2010) [8]. The indirect effect of extending influenza vaccination to school-aged children was demonstrated in Japan, where disease incidence in the elderly decreased in the years of universal immunization offer, but increased again when the school programme was discontinued [9]. Similarly, an age-based approach to pneumococcal vaccination using conjugate vaccines is likely to impact substantially more on morbidity than a risk-based-only strategy, if a coverage similar to that obtained with influenza can be foreseen [10]. *Streptococcus pneumoniae* contributes to the overall morbidity due to community-acquired pneumonia for more than two-thirds of patients when we consider known aetiological agents [11]. In some countries (like the USA), a high coverage with pneumococcal vaccination in infancy caused a decrease in the incidence of invasive pneumococcal diseases in the elderly as well, through a clear herd protection effect [12]. However, an impact on community-acquired pneumonia cases, although possible, is probably not as relevant, because of the greater amount of antibodies needed to prevent non-invasive pneumococcal diseases compared with invasive ones [13]. For this reason, an age-based plus risk-based approach to adult and elderly pneumococcal vaccination seems advisable.

A third vaccination is needed in the elderly population, that against herpes zoster and its most dreadful complication, post-herpetic neuralgia, which can heavily impair the quality of life of those affected (up to 12% of herpes zoster patients) [14]. Also in this case, because risk factors are almost impossible to predict, a single cohort or multiple cohorts age-based approach seems to be the most suitable to protect an aging population.

Vaccinations Needed due to Changing Disease Epidemiology

Adults have become one of the most important targets for vaccinations that were traditionally administered only to infants or children. The maintenance in many countries for several years of low coverage with the measles–mumps–rubella vaccination has brought about a progressive increase of susceptibility in adolescents and adults. This in turn has led to outbreaks in adolescents and adults in general, and especially in some settings, such as hospitals [15]. It is clear today that a catch-up programme in adolescents and adults is an indispensable supplement to immunization of toddlers and children with measles–mumps–rubella if elimination goals are to be reached in Europe in the next few years. Susceptibility has also shifted to older ages for hepatitis A, because of the progressive improvement of environmental sanitation; therefore hepatitis A has become an adult infection, not only of travellers [16], but also of clients of exotic food restaurants. Pertussis has also become a disease of adults, especially because immunity is not lifelong, with consequent possibility of experiencing several infections during life. In addition, infected adults can transmit pertussis to infants, who are at risk of severe consequences. This is the basis for the so-called 'cocoon strategy' aimed at supplying protection to the newborn through the immunity of parents and relatives [17].

Economic and Organizational Issues of Adult Vaccinations

A complete evaluation of HTA aspects of adult vaccination is needed to show that immunization is often cost-effective and sometimes cost-saving for the healthcare system. An attempt to assign scores in a semi-quantitative way to different interventions (taking into account not only cost-effectiveness ratios but also the total burden of disease avoided) showed that not only childhood vaccination series, but also influenza immunization of the elderly rank among the highest priority interventions to be implemented [18]. In other words, the belief that health promotion 'is not worth it' for older people is out of date: as people live longer, there are more years for older people to benefit from health promotion/disease prevention activities.

The concept of 'successful aging' means that older people no longer have to be willing to accept declines as the inevitable consequence of age.

Conclusion

The future of vaccination is lifelong vaccination. To achieve good uptake at all ages, we need to invest in communication activities to show that vaccine-preventable diseases can occur at any stage of life, and can be more serious in adults and the elderly. Every country should find different solutions (according to the national healthcare system organization) to finance, promote and administer all vaccines indicated at adult age.

Also, the economic convenience of such an approach should be shown based on local studies. We must also be aware that vaccination is more a global social process than an isolated medical action, based on the notion of community good or benefit, the relationship between the individual and the community, citizen and state, and health and disease.

Quoting the old physician Bartolomeo from Salerno (12th century), today it is true that 'practical medicine is divided into two parts: a science that preserves health, and one which cures disease… To preserve health is a thing that can be done better and with more certainty than restoring health once it has been lost'.

Transparency Declaration

PB received funds from different vaccine producers to support epidemiological and economic studies on vaccine-preventable diseases, and participatied in scientific boards supported by vaccine producing companies.

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