EXPERT REVIEWS

Herd immunity: recent uses in vaccine assessment

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Human communities defend themselves against specific infectious agents in a way that extends beyond the simple sum of the immune status of its individuals. By analogy with individual immunity to specific agents, the community level of immunity may vary from complete susceptibility to full protection. Herd immunity has been used to name this community property, which is the result of evolution through natural selection, leading to relationships between two species, typical of prey–predator systems. Varying uses of the term herd immunity led to the use of other expressions, such as herd protection, herd effect and community immunity. Knowledge derived from observational studies and models on herd immunity has supported decisions on the choice of vaccines and vaccination strategies for the benefit of populations. This knowledge is most likely to be extended in the future, with far-reaching effects.

Keywords: community immunity • herd effect • herd immunity • herd immunity threshold • herd protection • vaccination

The herd immunity (HI) effects observed under natural conditions, and the theoretical developments trying to explain those effects, led to the logical step of considering how it 'works' [1] under the influence of public-health interventions, such as vaccination, and how it may be used for the benefit of populations [2,3].

Looking for the most recent trends in the subject, Medline was searched for articles published from January 2004 to April 2008, in English, French, Portuguese and Spanish, using the key word 'vaccination' in combination with 'herd immunity' or 'herd protection' (HP) expressions. Some papers discussed general methodological aspects while others mentioned potential HI effects of vaccination in the context of specific target diseases.

As in a previous review on HI, it was verified that the expression 'herd immunity' was used by different authors for different ideas [4].

The concept of HI

Immunity can be defined as the capacity of an individual to recognize foreign substances (antigens) and promote a response, leading to their elimination [5]. 'Immunity' originated from the Latin word *immunis*, applied to tax-free individuals and to people protected or with privileges in relation to the remaining community [5]. These Roman uses of the word immunis have an analogy with our subject, 'HI'.

Mammals have an adaptive immune system, developed during evolution; great specificity and memory are its hallmarks [6]. These properties are central to the practice of vaccination [6]. While making great concessions to the complexity of biological events, we may try a simple conceptual approach considering that, after contact with a certain infectious agent (or part of it), it is possible that a single human being develops the capacity of reacting more efficiently to further attempts (memory) of 'aggression' by that infectious agent (specificity), in such a way that the agent and its deleterious effects are completely neutralized. Thus, 'immune' can be seen as a biological status observable in individuals in relation to specific infectious agents. This oversimplistic immunity model assumes a binary variable, with the values 'immune' and 'susceptible' to a specific agent, and is a useful tool for further discussions. It should not lead us to ignore the complexity of immune responses and that "different infections and vaccines can induce different degrees of protection against infection, against disease and against infectiousness and that these different sorts of immunity can wane or be boosted over time" [3].

Now let us extend the previous simplistic immunity model to a human community, with immune and susceptible individuals. The probability of an immune individual becoming infected with the specific agent is zero. The

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probability of the same event in a susceptible individual is between 0 and 1, and depends on several factors, such as the biology of the infectious organism and the host [7]. However, besides these factors intrinsic to the infectious agent and the host, the dynamics of the infection in that community depends on the proportions of immune and susceptible individuals and their distribution. The probability of infection of a susceptible individual is influenced by the proportion and distribution of those who are immune at each moment. In other words, immune individuals indirectly protect every one from infection, including susceptible people. At the limit, the proportion of immune people (and their distribution in the community) can be such that a specific infectious agent cannot enter and spread in a human population, even though a certain proportion of individuals of that community are still susceptible to that agent. In this situation, it is theoretically possible that a susceptible individual can be infected from an external source but it will not lead to the spread or 'invasion' of the community by the infectious agent.

Thus, human communities have levels of 'immunity' against specific infectious agents that extend beyond the sum of the immune status of its individuals. By analogy with individual immunity to specific agents, that community 'level' of immunity may vary from complete susceptibility to full protection. HI (along with other expressions) has been used to name this community 'property' that, in my view, is the result of evolution through natural selection, leading to relationships between two species, typical of prey–predator systems [7]. Also at the community level, simplistic all-or-nothing models usually do not fit the reality well: the complexity of individual immunity adds to the complexity and heterogeneity of human community structures and behaviors [2,3,7], resulting in a large variety of 'relationships' between specific human communities and infectious agents. I believe that different authors refer implicitly to those global properties of the community in relation to infectious agents when they use the expression HI or similar ones. I also believe that misunderstandings result from the fact that the expression HI has been used by several authors while studying and/or discussing partial aspects of the 'whole picture', such as the indirect protection afforded by those individuals that were not vaccinated.

Scientists can study matter organization at different levels and new laws emerge when we move into a higher complexity level. For example, a cell has new properties compared with those observed for molecules that make up the cell. This is similar with HI: it results from properties intrinsic to the infectious agent and the host but, at herd level, new relationships emerge. At both levels, scientific laws try to explain the observed reality.

Definitions & uses

The expression 'herd immunity' has been used since 1923 (Topley and Wilson, quoted by Fine [3,8,9]), and its concept has been discussed in some excellent review articles [2,4,7,8], book chapters [3,9] and other published papers and letters [1,10–12].

The theoretical work, using mathematical models, has made important contributions to the understanding of phenomena related to HI. The reader is encouraged to follow the sound explanations provided in the articles and book chapters quoted in the previous paragraph. Let us just raise some typical issues. Public-health practitioners and all those professionals involved in the design and implementation of vaccination programs would like to know the proportion of individuals that need to be immunized against a specific agent to prevent its invasion and spread in a human community [13]. Some authors have warned that the question has no straightforward and/or easy answer for several reasons [2,3,7], but theoretical work has been engaged in estimating such a magic proportion for specific infectious agents and named it herd immunity threshold (HIT) [3,13].

Precise values of HIT apply to randomly mixing populations (an assumption difficult to meet in reality) and infectious agents to which the simplistic immunity model mentioned previously is accepted. HIT can be estimated numerically from other measures, such as the 'epidemic threshold' and the 'basic reproductive number' [3,8,9]. In my opinion, the most interesting one is not the numeric formulas that express that relationship but the fact that all measure the equilibrium (or rupture of it) between a predator (e.g., a virus) and a prey (human). For example, HIT is shown to be related with the basic reproductive number (R_0), which is defined as the 'average number of secondary cases produced by one primary case in a wholly susceptible population' [7]. The larger the R_0, the higher the coverage needed to eliminate the infection [7]. Since HIT could be calculated as $[1-(1/R_0)]$ [3,7], efforts were made to estimate R_0 for specific infections and then derive and tabulate the corresponding HIT values [3]. HIT is then defined as 'the proportion of immunes in a population, above which the incidence of infection decreases' [3,8]. Some authors have alluded to the fact that such questions raised above 'what is the proportion … to prevent invasion…?' are not answerable in absolute terms, simply because of heterogeneities in human populations [3,7]; moreover, the use of HIT estimates to set up elimination targets has had little practical use in vaccination programs and crude estimates are naively optimistic in practice [3]. Beside these limitations and the lack of precision in estimates, the concept of HIT is nevertheless useful "for predicting the impact of a vaccination program" [3] and a 'good guide' for clues on the relative difficulty of eradicating different infectious agents [7]. For example, if the infectious agent A has a higher R_0 value than agent B, A it is more difficult to eradicate through vaccination, which can be easily derived from the above expression HIT = $[1-(1/ R_0)]$. In other words, 'greedy' predators (high R_0 values) are more difficult to stop, although they take more risks from eating too many prey too quickly.

It has already been said that the expression HI has been used with different meanings. It was first used in the context of epidemics in laboratory mice: "…led us to believe that the question of immunity as an attribute of the herd should be studied as a separate problem, closely related but in many ways distinct from, the problem of the immunity of an individual host." (Topley and Wilson 1923, quoted in [3]). This early approach had put the emphasis on the distinctive properties of the group in relation to an infectious agent, by comparison with individual member's immunity. I must confess that I am particularly keen on this insight of 'immunity as an attribute of the herd'. They did not distinguish between direct and indirect protection originated from vaccination, but subsequently, some authors have used the phrase for the indirect protection afforded by the nonvaccinated [3].

In a review paper published in 1971, the definition of HI was taken from a dictionary as "the resistance of a group to attack by a disease to which a large proportion of the members are immune, thus lessening the likelihood of a patient with a disease coming into contact with a susceptible individual" (Dorland's *Illustrated Medical Dictionary* 1965, quoted in [2]). In the author's opinion "this concept is directly applicable only to randomly mixing populations" [2] and for that reason he explored the modeling approach proposed by Reed and Frost, and further developed by some of their students [14].

In another review paper, published in 1990, with special emphasis on mathematical models [7], HI is not defined explicitly; nevertheless, it is initially suggested that it refers to the "effects upon population level" of immunization policies, while later it implicitly assumes HI to be what has been defined previously as HIT. This author highlighted some ecological aspects of the HIT concept when he mentioned that some agents probably appeared in human populations only when agriculture began, and human communities were big enough to sustain transmission of some infectious agents. He also drew attention fto the analogy between host–pathogen associations in human health and other prey–predator systems [7].

In a key review paper published in 1993, Fine quoted previous definitions and explained how the study of HI had previously led to different interpretations of quantitative and qualitative nature [8].

In 2000, John and Samuel quoted previous different definitions of HI and argued in favor of the need of a new precise definition [4]. They proposed HI "defined simply as the proportion of subjects with immunity in a given population" and a new term 'herd effect' was "introduced to denote the perturbation, if any, on the incidence of disease or infection in the unimmunized segment of a population, induced by herd immunity of immunization" [4].

A dictionary of epidemiology, sponsored by the International Epidemiological Association [13], included the different meanings historically given to HI rather than a unique definition.

In another attempt to precisely define epidemiological terms, in 2004, Paul described the difference between HI and HP [11]. He argued that immunized people provide additional benefits to the community in two different ways, namely HI and HP. HI would correspond to the spread of the attenuated agent (bacteria or virus) used in the vaccine from the immunized to the unimmunized individuals, resulting in the protection of the latter, while HP would apply to the indirect protection of the unimmunized because immunized individuals lead to the break of the transmission chain or decrease the probability of contact with the infectious agent of those not vaccinated [11]. The author listed classical examples of vaccines able to induce both effects (oral polio vaccine), HP only (inactivated polio vaccine) or no benefit at all to the unimmunized (tetanus toxoid vaccine).

In the book *Vaccines*, the chapter on HI issues published in 2004 [9] and 2008 [3] was named 'Community immunity' by suggestion of the editors (Plotkin and Orenstein). This is a change from the famous review article on 'Herd immunity: history, theory and practice' published by Fine in 1993. In 2008, the opinion of the authors of that chapter, on the issue of different uses of the expression HI, is most interesting: "this review avoided emphasis upon a simple interpretation of herd immunity, instead accepting the varied uses of the term by different authors"; they went on explaining that "this is in keeping with the first published use of the term, which posed the problem of herd immunity as the problem of how to distribute any given amount of immunity (e.g., antibodies and vaccinations) so as best protect a population from disease" [3].

This issue of the use of specific words or expressions with or without precise definitions has raised passionate discussions. For example, the approach used by Fine (see previous paragraph) has been criticized by those who feel that HI definitions are not clear, precise or complete; nor do they agree among themselves. A precise definition is necessary. We do not favor the *status quo* approach adopted by one reviewer [4]. However, equally strong opinions have been expressed against the emphasis put on the meaning of words; Popper argued against taking too seriously the issues on words and their meanings; instead, he supported that what should be taken seriously "are facts and statements about them: theories and hypothesis…" [15].

By the very nature of the Medline search performed here, the articles quoted used the terms HI or HP. Authors tended to prefer one or the other, sometimes with different meanings, and sometimes indistinctly (and so is often done in this text). The meaning varies from the general global properties of the community in relation to infectious agents mentioned previously, to the more specific meanings of herd effect and HP proposed in 2000 [4] and 2004 [11], and described in previous paragraphs. The most common use was that meaning the effect of vaccination on unvaccinated members of the community, but sometimes HI was used just as synonymous to HIT. I tried to describe faithfully what the authors meant (facts and theories), and distinguish it clearly from my personal interpretations, whenever they are expressed. Attempts to reach a consensus on precise definitions were not within the scope of this review.

General methodological issues (articles published 2004–2008)

The papers identified were grouped in the following areas: mathematical models, economic evaluations of vaccination programs, vaccination ethical issues and vaccination strategies.

Mathematical models

There is a long tradition in the development of mathematical models to "elucidate the reasons for epidemics and/or to predict the behavior of the disease consequent to given control measures"[13], such as vaccination. Following that line, some articles were published in recent years address specific methodological issues related to HI/HP effects.

The minimum proportion of immune individuals in a community that can result in a decrease in incidence (HIT) depends, among other things, on the transmission pattern [13]. Some researchers have explored theoretical aspects of contact networks [16], concluding that their heterogeneity may have consequences on the effect of HI induced by natural immunity or vaccination. For example, in communities with heterogeneous contact patterns, random vaccination may result in lower community protection than natural immunization due to epidemics [16]. Heterogeneity is also observed in vaccine uptake behaviors [3], and has been included in some models using game theories [17,18].

A literature review on the use of mathematical models to simulate vaccination strategies, taking into account HI, raised interesting methodological challenges and promising uses of this approach to answer questions such as 'Is there optimal vaccination coverage?' and 'is it possible to achieve optimal coverage through individual choices?' [19].

Economic evaluations of vaccination programs

Three articles have addressed the methodological issues of economic evaluation of vaccination programs [20–22]; and although some specific diseases were addressed, they were used merely as examples to illustrate methodological discussion. There is a longer tradition of this type of study for vaccines than for classical medicines [22]. Although there is some specificity concerning the models used in the economic evaluation of vaccines, the more relevant for this review is HI.

Cost–effectiveness analysis (CEA), and the similar cost–utility analysis, are particular types of economic evaluation that have become the most used approaches in the economic evaluation of public-health interventions, such as vaccination [20].

Among other reasons, the increasing number of CEA studies on vaccination stems from escalating healthcare costs [22], new (and expensive) vaccines [20] and the request of decision makers to compare vaccination with alternative use of resources [20].

The authors agree on the need to take HI into account, in order to have more complete and valid estimates of all effects of vaccination [20,22]. In some cases, the indirect effect of vaccination (HI) among nonvaccinated people can be greater than the direct effect on the vaccinated individuals [21]. In order to incorporate HI into the analysis, dynamic (instead of static) modeling approaches must be used [20,21], which has not always been the case in the literature [20].

Vaccination ethical issues

Some have raised the 'prevention problem' against vaccination, arguing with the supposedly inequitable distribution of benefits and risks resulting from preventive medicine's interventions [23]. However, HP is an important public-health good for all members of society and so it has been argued against the ethical legitimacy of the 'prevention problem' argument [23].

The rise in the proportion of unvaccinated individuals resulting from religious and philosophical exemptions to mandatory vaccination has been a cause for concern in the USA; furthermore, 'exemptions of convenience' have been observed [24,25]. Therefore, arguments in favor of more strict control procedures for exemptions have been put forward, in order to balance individual rights with the need to preserve HI/HP, a common good [24,25].

The HI/HP effect has also been used as an argument in ethical discussions on the individual's duty to vaccinate versus the right to refuse vaccination among certain population groups, such as international travellers [26] and nursing home residents [27]. The potential benefit to the community and to the vaccinated individual argues in favor of mandatory vaccination when weighed against the risks [28].

Vaccination strategies

Vaccination strategies may have different effectiveness in inducing HI/HP beneficial effects. For example, who should be vaccinated in case of vaccine shortage [29]? Should we vaccinate high-risk groups or those within specific age and/or socioeconomic groups? Some authors have explored mathematical models to compare those different strategic options. One example was influenza vaccine; shifting the traditional priority from high-risk individuals to those individuals with occupations with many daily personal contacts will result in a better HI/HP effect, which may be more useful to the population as a whole, and also for the high-risk groups themselves [12].

Furthermore, for some target diseases, it is now clear that pediatric vaccination programs have brought benefits for adults in the community [30]; some of these benefits may have a HI/HP effect back to infants and young children [30].

Since vaccination coverage is a paramount determinant of artificially induced HI/HP, the identification of factors affecting vaccination coverage is essential to choose the most efficient vaccination strategies. Some studies have highlighted the influence of literacy, religion and culture on vaccine uptake [31]; indigenous ethnic minorities have also been a case for concern [32]. In all instances, the main recognized point is that low vaccine coverage and heterogeneous vaccine uptake have a negative HI effect [31,32] and need to be considered in the choice of vaccination strategies.

The choice of mass campaigns or routine vaccination may be influenced by the prospect of better and/or faster benefits resulting from HI effects [33]. The choice of one of those strategies or a balanced combination of both will continue to be a dilemma in future occasions.

As mentioned before, HI/HP effects also depend on the pattern of transmission of the infectious disease. Thus, it is no surprise that vaccination against sexually transmitted diseases might need specific strategies (who and when to vaccinate?) to optimize HI effects [34].

Effects induced by vaccination against specific target diseases (articles published 2004–2008)

The HI/HP effects induced by vaccination have special features, depending on the specific target diseases. In recent years (2004–April 2008) much attention has been paid to the indirect effects of conjugate vaccines against *Streptococcus pneumonia* (pneumococus) and *Neisseria meningitidis* serogroup C (meningococcus C), reflected by 34 and nine published articles, respectively. Reviewed papers in the following subheadings focus on specific diseases and refer to their particular HI/HP effects; but some of them discuss interesting general methodological issues that extend beyond one specific target infectious agent. Four target agents/diseases were not discussed in this review (diphtheria, hepatitis B, meningococcus A and meningococcus B) because too few papers were identified in the considered period (2004–2008).

Vaccination against the specific target diseases in the following subheadings has been discussed in many articles, including review papers. This review does not cover all issues, only those related to HI/HP effects.

Bordetella pertussis

The effect of HI/HP after large-scale vaccination for many years has been verified, leading to dramatic worldwide decreases in the incidence of infections due to *Bordetella pertussis*, mainly in childhood [35,36]. Nevertheless, that effect was not enough to eradicate the infection and disease and a recrudescence of pertussis has been observed in adolescents, adults and infants [35,36], some of them too young to have been efficiently immunized by vaccination, and more prone to develop whooping cough syndrome and a more severe illness. Most of the time, *B. pertussis* has been transmitted to very young infants by adults [35–37], namely close relatives such as mothers [35]. Thus, the probability of that transmission pattern has changed because of an apparent increase of infection incidence among adolescents and adults. Phrasing it differently: the partial HI/HP effect, induced by childhood vaccination for many years, was enough to control the disease among children but not sufficient to eliminate the infection, especially among adults; subsequently this raised the probability of transmission between adults and very young children.

One of the reasons put forward to explain this epidemiological pattern is waning immunity. Protection induced by natural infection or vaccination wanes with time but the time course is not well known [36]. As a consequence, several authors have proposed vaccination strategies with booster doses of vaccine, given to adolescents and adults [36,38–40]. A variation on this strategy was advocated: the priority should be to vaccinate adolescents and adults who are in contact with young infants, such as parents, grandparents and health workers [36]. A particular recommendation was to vaccinate mothers [36] and households of pregnant women [37]. All those alternatives aim to protect infants too young to be fully vaccinated, immunizing those likely to transmit the disease to them (a paradigmatic example of the deliberate use of the HI/HP effect) [37,41].

Some particular features of this disease and corresponding immunity raise methodological obstacles to the assessment of HI/HP effects. The nonspecific clinical manifestations of the infection among adults make an etiological diagnosis difficult. Furthermore, seroepidemiological studies to assess HI face the problem of the lack of reliable serological correlates to immunity [37].

Another potential obstacle to the induction of HI effect is vaccine efficacy. This problem was raised in relation to the new generation of acellular vaccines but some researchers found evidence to support optimism in this issue [39,40,42]. Using innovative approaches and interpretations of mathematical models, some authors have argued that, above a certain level of transmission intensity in the community (reinfection threshold) [43], the interruption of transmission would require a vaccine that confers more protection than that induced by natural infection or, ideally, life-long protection [44]. Some authors have proposed a new and improved vaccine using a genetically inactivated pertussis toxin, with the aim of increasing immunogenicity and duration [45].

The validity of conclusions from CEA of new vaccination strategies, with booster doses in adults, may be affected by some of the specific methodological problems mentioned previously because cost–effectiveness depends on the incidence among older age groups and the duration of immunity induced by vaccination [36,38,46].

Cholera

Killed oral cholera vaccines have been licensed and used internationally for adults and older children [47], and recent papers have passed the opinion that they can induce an important HI/HP effect with a potential large public-health impact [47–49].

In order to assess this potential HI/HP effect, studies with two different methodological approaches were carried out [47,48]. The impact among children less than 2 years of age, who were too young to be vaccinated, was assessed using an individually randomized, placebo-controlled trial; they did benefit from vaccination of older children but the most pronounced indirect protection resulted from the vaccination of adult women [47]. Another approach was simulation using a stochastic mathematical model [48]. The model predicted a large beneficial impact to the whole community (vaccinated and unvaccinated) depending on the prior immunity in the population and the vaccination coverage reached [48].

Haemophilus influenzae *type b*

Very few recent articles have covered exclusively issues related with this target disease. The vaccine against this agent is generally mentioned in the context of papers on vaccination against meningococcus C and pneumococcus (the new 'fashion' vaccines), because it was the first conjugate vaccine used in large-scale immunization programs. The success of the vaccine against *Haemophilus influenzae* serotype b (Hib) in the reduction of the disease burden was due partially to the ability of conjugate vaccines to induce HI/HP effects through the reduction of nasopharyngeal carriage [50,51]. Nevertheless, important gaps remain in the knowledge of immunity induced by conjugate vaccines [50].

Two recent articles have used different methodologies to assess specific aspects of this vaccine. A statistical model was used to analyze historical data of the disease in Brazil, concluding that the vaccination program extended its benefits to age groups that had not been vaccinated [52]. In the UK, Hib conjugate vaccine was used in a booster campaign that re-established HI/HP levels. To assess that effect, active epidemiological and laboratory surveillance was used [53].

Hepatitis A

The vaccine for hepatitis A introduced in the 1990s and recommended for individuals at high-risk of exposure [54,55]. Socioeconomic improvements can reduce the levels of endemic hepatitis A [56] and seroprevalence is low in industrialized countries, meaning that international travelers from these countries to high endemicity areas are considered high-risk groups for the purposes of vaccine recommendation [57].

Meanwhile, in countries with intermediate endemicity, the decrease in incidence may be followed by an increase in the clinical burden of the disease among adults [56,58] because of the shift in the median age of incidence.

The high-risk strategy was not expected to produce any significant impact at population level [55], but the magnitude of the HI/HP effect of vaccination was surprisingly large when vaccination strategies, with broader population groups covered, were implemented. Due to the direct and indirect effects (HI/HP), dramatic decreases in incidence were observed after vaccination programs in Israel [59] and regions of other countries [55,60,61]. The success of the vaccination programs was marked, even with modest vaccination coverage [61] and without catch-up strategies [59], leading to optimistic opinions such as "it is now even conceivable to eradicate hepatitis A virus" [55].

Some authors believe that in the poorest countries, where people are infected at very young ages, mass immunization with hepatitis A vaccine will remain a low priority for some time [61], but such an important HI/HP effect has been integrated in the predictions of mathematical models [62] and economic analysis [56,63] and supported the decision of national universal vaccination programs [56,62].

Thus, hepatitis A vaccination is an example of underestimation of an important HI/HP effect that, after being observed, assessed and integrated in economic analysis, strongly influences decisions on vaccination strategies.

Human papillomavirus

Vaccination against some subtypes of human papillomavirus has recently been the focus of intensive attention and many studies. Excellent reviews have been published on this subject [64,65] along with controversial debate [66]. Official bodies, such as the European Centre for Disease Prevention and Control (ECDC) have issued detailed information and guidelines on the use of these vaccines as a potential tool to prevent cervical cancer [201]. One of the discussed issues is the potential of these vaccines to reduce transmission and induce positive HI/HP effects. It was concluded that it is "likely" but "there is as yet no direct evidence" that is dependent on ongoing and further research [201].

Alhough not proven directly, potential indirect protection of unvaccinated people has been integrated into theoretical mathematical models to simulate the impact of vaccination [67,68]. When modeling is performed to assess cost–effectiveness, the logical result is that the inclusion of the HI/HP effect ('there is as yet no direct evidence') leads to conclusions favoring the use of large vaccination programs [69,70]. Modeling has also been used to simulate possible HI effects of vaccinating males or high-risk groups, with different strategies; most simulations have not shown important advantages compared with the vaccination of young females (with high coverage) [201]. Assumptions are a key aspect in the validity of the conclusions drawn from modeling. If assumptions are wrong, the results will be far from reality. Far too many optimistic assumptions have been made. On the other hand, the time lag between vaccination and effect on cancer, and the changing quality of screening programs, should be better assessed, for example in opportunity cost terms. Maybe HI is not the main actor in this 'drama'.

Influenza

Selective vaccination of schoolchildren against seasonal influenza results in the indirect protection of other age groups, such as adults, with reduced incidence of the disease. This HI/HP effect was verified in observational studies in areas where this strategy was implemented [71], in vaccine trials [71,72] and in simulations with mathematical models [73]. Vaccination of nursery children could be beneficial for this age group and result in an indirect effect to the community. A study was performed to assess uptake and acceptability of such approach. Low uptake and acceptability were observed. Parents' balance toward influenza vaccination clearly favored a direct benefit to children in relation to a potential HI effect [74].

In the case of pandemic influenza, the US health services have planned the distribution of prepandemic vaccines by the states with a *pro rata* criterion. An alternative approach was simulated, showing that a discretionary strategy with allocation of more vaccines to certain regions, in order to reach HI/HP levels there, would have a better overall national impact in terms of the number of infections averted. An intermediate strategy (50% discretionary) was also simulated but the results are sensitive to parameter values that cannot be foreseen with certainty [75].

Measles

The need of high vaccination coverage in order to immunize the proportion of people in the community necessary to stop transmission (HIT) is generally accepted in the scientific community. That is reflected in the fact that recent articles no longer approach methodological issues related to estimates of HIT, but focus on the analysis of measles outbreaks in the light of the HI/HP concept.

In countries such as Iran, measles transmission had not been interrupted in the period 2000–2002 and concern was directed at the vaccination strategies needed to reach HIT [76]. Other countries are in more advanced stages, and measles outbreaks were observed after 'honeymoon' periods [77,78]. In Singapore, the strategy to reach and sustain HI against measles includes different simultaneous approaches, such as serological surveys, improved vaccination coverage and measles surveillance [79].

In developed countries, some specific constraints have kept vaccination coverage below HIT levels. That was the case of adverse publicity against the measles–mumps–rubella vaccine in Scotland [80].

A particularly interesting analysis of the situation in The Netherlands, where high but heterogeneous vaccination coverage was reached. In these situations, measles transmission can be interrupted without solid HIT but outbreaks can then occur after reintroduction of the virus in the community. Modeling can be undertaken to simulate such situations, incorporating coverage levels and heterogeneities [81].

Meningococcal C disease

After the success of the conjugate vaccine against Hib, this was the 'next' conjugate vaccine to be used in large vaccination programs. Some review papers have approached conjugate vaccines and meningococcal vaccines from a general perspective, rather than addressing specificities related with meningococcal serogroup; that general perspective includes the HI/HP concept and its consequences [82]. Many impact observations have come from the UK, where a comprehensive program has been implemented [83], using meningococcal serogroup C conjugate vaccines (MCCVs). Besides high effectiveness among vaccinated individuals [84], MCCVs were associated with important reductions of *N. meningitidis* serogroup C (or meningococcus C) carriage in different age groups, which is consistent with HI/HP effect [83] and has been observed in other European countries [82].

These observations have been incorporated into special mathematical models used to simulate the impact of different vaccination strategies [85]. Exploring these models has demonstrated that impact results are particularly sensitive to parameters such as duration of protection and efficacy of vaccination against carriage acquisition [85].

The observed effects of vaccination and the initial development of mathematical models led to the systematic incorporation of HI/HP effects in the models used to assess economic aspects of programs using MCCVs [85–89]. It has been concluded that should HI/HP not be included in the analysis, there would be an underestimate of the impact of MCCVs, possibly affecting decisions on vaccine strategies [86].

Mumps

Even after the mass use of vaccination against mumps, several outbreaks have occurred. Although the relative contributions of the putative causes put forward to explain this are unclear, the first explanatory hypothesis for the moderate effectiveness of mumps vaccines during outbreaks was insufficient HI in settings such as schools and college campuses [90].

The HIT level for mumps has been estimated to be in the range of 70–90% [90]. Results of national serosurveys were used to estimate whether a country is below the HIT [91].

Taking into account the estimated HIT and the observed low effectiveness of the vaccine, it has been stated that a two-dose strategy might be needed to achieve HIT [90], and a catch-up strategy to give the second dose has already been tried, with the explicit aim of achieving HIT, particularly in higher risk settings [92].

Pneumococcal disease/conjugate vaccines

A review paper on the impact of these vaccines in the USA was published recently in this journal, covering several different issues, from the analysis of the epidemiology of the target disease to the characteristics of the vaccine and its impact, both on the disease and on the carriage of the bacteria; the HI effect was verified in observational studies [93]. In a further 33 articles, published between 2004 and April 2008, HI or HP in relation to heptavalent pneumococcal conjugate vaccines (PnCV7) was mentioned by the authors when tackling issues such as comparison of vaccination policies among countries [94], mathematical models to estimate the impact of vaccination [95,96], economic assessment [97–104], replacement of serotypes [105–110], special clinical conditions [107,111–114], nasopharyngeal colonization [115,116], impact assessment using analytical epidemiology studies [117], impact assessment using descriptive epidemiology studies [118–123], and pre-vaccination laboratory surveillance of invasive pneumococcal disease (IPD) [124].

One paper compared vaccination policies among European countries [94], while discussing the decision process. It was concluded that factors that will influence national decisions on the implementation (or not) of universal vaccination programs will be the 'local disease burden' and potential impacts of serotype replacement and HI (defined as the indirect protection to the unvaccinated) [94].

Mathematical models were used to estimate the impact of vaccination. For example, one model was developed explicitly to estimate 'herd (indirect) effects' with local data from the USA [95], while in Scotland the potential impact on IPD was estimated before the vaccination program was in place, and the potential HP effect among adults was integrated in the model [96].

The economic assessment of vaccination strategies with PnCV7 has been the subject of several recent articles, leading to the publication of reviews [98,101] and typical CEA applied to the specific epidemiological situation of countries such as Germany [97,99], The Netherlands [100], the UK [103,104] and the USA [102]. One of the papers described the development of a 'web-based user interface' that allows the users to build different scenarios and perform CEA [100]. In all these CEA studies, the inclusion of potential HI/HP effects in the analysis changed cost–effectiveness in favor of vaccination. Another critical factor is the number of doses needed to induce protective immunity in each vaccinee; in some situations, the difference between four and three doses may be decisive in terms of concluding whether PnCV7 is cost effective [101].

The combined direct and indirect effects of vaccination, leading to reductions of vaccine-type pneumococcus (VTPn), may be followed by the 'replacement' by other serotypes (nonvaccine type pneumococcus [NVTPn]). This has been mentioned in review articles [105,108,110,125] and specific studies using methodologies such as community-randomized trials [106,109]. Replacement has been perceived by some authors as a threat to the success of these vaccines [105], but others have a more optimistic view of this effect, arguing that a vaccine acts as a 'serotype filter' with "little effect of genetic background" [109]; thus, the effect of vaccination on strains with drug resistance or high virulence would not be countered easily by replacement. Some limitations to desirable HI effects do not result from replacement, but from the fact that predominant serotypes among the elderly are not those included in the PnCV7 [107,126]. Studies on the impact of replacement in the USA have reported extreme conclusions from "no evidence of any concomitant increase in pneumococcal disease caused by nonvaccine serotypes" [121] to the "substantial increase in NVTPn invasive diseases in Alaska Native children" [127]. Overall, in the USA, the net balance between the benefits of PnCV7 vaccination and the negative impact of replacement is beneficial, up to this moment [3,93], although it is not known whether that will be sustained in the future. Elsewhere, the observed balance seems even: global IPD incidence in Portugal before and after the introduction of PnCV7 vaccination "did not change significantly" [128].

The issue of different use of terms to explain epidemiological patterns was approached in the beginning of this article, and different definitions of HI and other expressions were transcribed. We see here a modern version of this old recurrent problem of the use of terms. Vaccinating against some serotypes of an infectious agent results in decreases in the incidence of disease (and carriage) by those serotypes, balanced by increases in nonvaccine serotypes. Why does the scientific community call the first 'HI' and the second 'replacement'? Are they not the two faces of the same coin? Maybe we are missing an ecological insight of the problem. Maybe this bacteria has been here long before humans and was selected alongside our ancestors. The result is the existence of 90 serotypes, with a large capacity to invade ecological niches and the ability of humans to, most of the time, live with the potential predator without being 'eaten'. We must pay attention to the mounting evidence and discussions being published on replacement.

Some special clinical conditions are associated with higher risk of complications in the event of pneumococcal disease, and lead to the logical recommendation to vaccinate these high-risk groups due to the expected direct benefit of being immunized. Furthermore, the indirect HI/HP effect of vaccination programs is accounted for the decrease of pneumococcal disease among clinical conditions, such as sickle-cell disease [111] and HIV infection [112,114]. Nevertheless, some authors have expressed their opinion against vaccination strategies targeting high-risk groups only [99,113], arguing that they may be insufficient to induce relevant HI/HP effects [113].

PnCV7 vaccination is highly efficient in preventing serious disease caused by VTPn, but the prevention of nasopharyngeal colonization (symptomless) is also an important mechanism, reducing the chances of spread of the infection and indirectly protecting from disease: HI/HP effects [116]. Although nasopharyngeal colonization is measured or discussed in papers covering wider issues, the recognition of the importance of that mechanism led to the publication of particular reviews [116] and specifically designed evaluation studies [115].

In order to assess the indirect impact of vaccination, a specifically designed analytical epidemiology study was used. This case–control study showed that adults with vaccinated children in the home have lower risk of IPD with VTPn [117].

In order to assess the indirect impact of vaccination, descriptive epidemiology studies were the most widely used. Studies used data from surveillance systems, either hospital [119] or population based [118,122], while other researchers opted to collect information from different specific studies and then publish review analyses [120,123]. The observation of the beneficial impact of PnVC7 vaccination programs among nonvaccinated individuals is consistent throughout all studies, independent of the methodological approach or the epidemiological setting. Furthermore, several authors have emphasized the extreme importance of surveillance in the monitoring of the different aspects of impact of such vaccination programs [93,98,118].

Recognizing in time the importance of surveillance, 'a comprehensive IPD laboratory surveillance program' was implemented in Australia [124], 2 years before the start of a universal vaccination program in young children, allowing reliable postvaccination comparisons.

Polio

For decades, the issue of HI/HP induced by vaccination was intensely debated concerning the relative merits of live-attenuated and inactivated polio vaccines in inducing HI/HP effects [9]. The development of a polio eradication program and the elimination of the disease from the developed world led to a change in the research agenda: for the period 2004–2008, only three references were found mentioning HI/HP and vaccination against polio [129–131].

Those articles deal with the concern of polio-free developed countries in preventing hypothetical importation and spread of wild polio. In the three papers identified, serosurveys were the tool to estimate if levels of vaccine-induced immunity were compatible with HIT levels [129–131]. Specific issues were raised, such as the recommendation to revaccinate adolescents in Greece [131] and Japan [129]. The lower level of immunity against type 3 virus is common to the published serosurveys [129–131].

Rubella

This is another target disease for which previous concerns and discussions on the importance of HI/HP effects induced by vaccination [9] have apparently 'waned' in recent years. Only two references were found mentioning HI/HP and vaccination against rubella [132,133].

Those articles deal with the concern of developed countries to reach and sustain HIT levels in order to prevent congenital rubella syndrome (CRS); in both cases, serosurveys were used as the assessment tool [132,133]. In the case of Israel, the decrease of immunity levels below HIT, with the consequent outbreak among young adults, seems to have been due to the widespread pediatric vaccination that was not followed with appropriate catch-up among adolescents and young adults [133]. In Taiwan, lower immunity among immigrants led to the recommendation to vaccinate foreign brides [132].

Rubella is a good example of the deliberate use of HI to our benefit. Young boys are vaccinated because they will help to interrupt transmission, eliminate the virus and prevent CRS; moreover, as adults they will indirectly protect their pregnant partners. However, rubella vaccination can be iatrogenic and raise the incidence of CRS if vaccination coverage is not adequate. Therefore, it sets an example: vaccination is not necessarily good; it can produce no effect or even cause harm.

Varicella

In societies without vaccination, natural infection confers immunity to such high levels that a partial HI/HP effect is induced among young adults, for example military recruits [134]. Severe cases and complications are more likely to occur below 1 year of age [135] and among adults [136]. Vaccination against varicella has been introduced in national programs of countries such as the USA [138] and Uruguay [138], and observations are consistent with a vaccine-induced HI/HP effect [136–139].

Assuming a HI/HP effect of varicella vaccination in those studies and their own observations, some authors have deduced recommendations, such as vaccinating older children to avoid transmission to babies [135] and two-dose schedules to provide sufficient immunity to the proportion needed (HIT) to prevent outbreaks in schools [137]. European national serosurveys were used to estimate the R_0 and the HIT, with the hope of providing useful information for the design of national vaccination policies [140].

It is relevant that none of the articles identified mentioned concerns expressed by other authors of potential adverse effects of vaccination on the incidence of herpes zoster [9]. These concerns are based on observational studies, but no solid evidence exists to predict exactly what will happen. Nevertheless, it is clear that ecology and immunity to this virus is complex and different from smallpox, polio or measles; and long-term implications of current vaccination strategies are unclear [9]. Uncertainty and risks may be assumed in epidemiology and public-health decisions [141], but what is striking in this case is the total ignorance of the concerns, expressed previously, in the recent papers addressing HI/HP issues of vaccination against varicella virus.

Is HI not about ecology? Is varicella a virus that appeared in human populations only when agriculture began [7]? Respiratory transmission seems an efficient strategy when human communities are big enough and many susceptible individuals (preys) are being born every year. However, this virus has the ability to survive in a dormant state for many years. Is this another survival strategy? How did we arrive at a situation with millions of humans with the dormant form of the virus? It seems to be an equilibrium state. Vaccination is a rupture in an equilibrium system, which we want to work in favor of human communities.

Expert commentary

The expression HI will continue to be used with different but related meanings. In order to clarify concepts, similar terms have become more popular, such as HP, herd effect or community immunity. Most often, they focus on the purpose of using vaccination to maximize the benefits to a specific population. To immunize 100% of the population through vaccination is impossible; first, to vaccinate 100% of people is very unlikely for logistic reasons, let alone contraindications. Furthermore, to immunize 100% of the vaccinated is very unlikely because there is no such a thing as an absolutely efficient vaccine. Even if there were unlimited resources, a decision would have to be made concerning whom to vaccinate first. From conception to delivery, decisions have to be made on whom and when to vaccinate, and which targets should be set for the program in a specific time frame. Those decisions include fundamental strategic options (e.g., aiming to control or eliminate a disease). The health professional has to decide on what to do for the benefit of the patient and should decide on the best available scientific evidence. Those responsible for vaccination programs have to take decisions equally well supported (evidence-based public health). The best decisions must take into account that the dynamics of infection and vaccination in a human community result in protection (or risk) to the whole community, including those not vaccinated: a HI effect.

It is necessary to approach human infectious diseases from an ecological view. Interpreting infectious diseases as part of survival strategies of humans and infectious agents will certainly give us a better insight about reality. The concept of "a biological balance between two populations (the host population and the parasite population)" was expressed a long time ago and its logical consequences explained [14]. So, although ecological insights have been around for many years, explaining why they seem to be ignored by an anthropocentric view in some very recent papers is a challenge for us all.

Vaccines have an impressive curriculum so far, but it should be kept in mind that vaccination has iatrogenic potential. Thus, understanding HI determinants and mechanisms will be essential to manipulate vaccination for the benefit of the population, while avoiding unwanted side effects.

Throughout this article, it has been clear that HI is important for new and old vaccines alike. What varies is the epidemiological situation, setting the priorities, and changing them with time and place. Unfortunately, too often, other less altruistic motives also set the agenda of vaccination committees and researchers. For example, the relative number of articles concerning a specific target disease should not be seen as a correlate to the public-health magnitude of the problems or the relative importance of HI for the success of vaccination.

I am a firm believer in evidence-based public health. To that purpose, sound learning of epidemiology is very important. In a book on the methodological aspects of teaching epidemiology, John Last wrote: "… good teaching … encourages a critical, sceptical attitude to dogma and *ex cathedra* opinion statements, and insistence on seeing the evidence for all conclusions" [142].

Five-year view

Improvements in the understanding of HI mechanisms and its use in vaccination programs are likely to be important in the near future and will follow three broad areas: basic immunology applied to vaccination, epidemiological studies and theoretical work using mathematical models.

Basic immunology applied to vaccination will better explain the immune responses and measure more accurately vaccine induced protection against infection, disease and infectiousness, and the mechanisms of waning and boosting immunity (both naturally and artificially).

Epidemiological studies (both experimental and observational) will measure the impact among vaccinated and unvaccinated people in a more valid and precise way; monitoring the impact of vaccination programs (indirect effects included) will improve significantly; the consensus among experts on the paramount importance of epidemiological surveillance will facilitate developments in this area; and laboratory techniques, pushed by advances in basic science, will play an increasingly important role in surveillance systems.

Theoretical work using mathematical models will help to improve our understanding of the dynamics of infection and immunization through vaccination, and provide us with the improved capacity of producing simulations available through software even to the 'uninitiated' in differential equations. Conceptual advances are also in the pipeline. We must be open to radical innovative approaches. In my view, an ecological approach to human infectious diseases, under the light of natural selection theories, is necessary; mathematical models are useful to explore such an approach.

The development of these three areas will provide powerful tools to aaply the knowledge on the subtleties of HI to the benefit of populations.

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Key issues

- Herd immunity expression has been used with different meanings by different authors but, in the end, it all comes to how best to use vaccination in order to maximize the benefits to populations.
- The relationship between a human community and a specific infectious agent has properties that extend behind the sum of individual immune status; that is at the core of the herd immunity concept.
- The herd immunity concept leads to that of a herd immunity threshold.
- Herd immunity threshold is 'the proportion of immunes in a population, above which the incidence of infection decreases'.
- Herd immunity threshold has been used as a tentative guide with which to set targets for vaccination programs.
- Human populations are not homogeneous, and specific heterogeneities influence herd immunity thresholds and the choice of the better vaccination strategies.
- There are reasons to be optimistic regarding future developments in the understanding and use of the herd immunity concept in vaccination programs.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1 Berger A. How does herd immunity work? *BMJ* 319, 1466–1467 (1999).

2 Fox JP, Helveback L, Scott W, Gatewood L, Ackerman E. Herd immunity: basic concept and relevance to public health immunization practices. *Am. J. Epidemiol.* 94(3), 179–189 (1971).

•• **First review on herd immunity. A seminal article, so considered by subsequent review papers.**

3 Fine PEM, Mulholland K. Community immunity. In: *Vaccines (5th Edition).* Plotkin SA, Orenstein WA (Eds). Saunders, Elsevier, PA, USA 1573–1592 (2008).

•• **The authors developed the basic ideas of a review paper published in 1993 and the previous edition of this book. New knowledge and new vaccines make it particularly rich. This text is an outstanding document.**

4 John TJ, Samuel R. Herd immunity and herd effect: new insights and definitions. *Eur. J. Epidemiol.* 16(7), 601–606 (2000).

• **The authors were especially concerned with the different uses of the term 'herd immunity'. The revision of previous definitions and the proposal of new ones is a good insight search on the subject.**

5 Forte WN. *Imunologia básica e aplicada.* ARTMED® Editora S.A., Porto Alegre, Brasil (2004).

6 Ada G. The immunology of vaccination. In: *Vaccines (4th Edition).* Plotkin SA, Orenstein WA (Ed.). Saunders Elsevier, PA, USA 31–45 (2004).

7 Anderson RM. The concept of herd immunity and the design of community-based immunization programmes. *Vaccine* 10(13), 928–935 (1992).

•• **Emphasis is placed on mathematical models as a tool to understand the effects of herd immunity.**

8 Fine PEM. Herd immunity: history, theory and practice. *Epidemiol. Rev.* 15, 265–302 (1993).

•• **A cornerstone on the subject.**

9 Fine PEM. Community immunity. In: *Vaccines (4th Edition).* Plotkin SA, Orenstein WA (Eds). Saunders Elsevier, PA, USA 1443–1461 (2004).

• **The author developed the basic ideas of the review paper published in 1993, but with new insights.**

10 Mühlemann K, Weiss NS. Can herd immunity influence the assessment of vaccine efficacy in nonrandomized studies? *Am. J. Public Health* 87(1), 113–114 (1997).

11 Paul Y. Herd immunity and herd protection. *Vaccine* 22(3–4), 301–302 (2004).

•• **Very important letter to the editor. The authors addressed the recurrent problem of the different uses of the term 'herd immunity'. While new definitions were proposed, a clearer view emerged.**

12 Tennenbaum S. Simple criteria for finding (nearly) optimal vaccination strategies. *J. Theor. Biol.* 250(4), 673–683 (2008).

13 Last JM (Ed.). *A Dictionary of Epidemiology. (4th Edition*). Oxford University Press, Oxford, UK (2001).

14 Maia JOC. Some mathematical developments of the epidemic theory formulated by Reed and Frost. *Hum. Biol.* 24, 167–200 (1952).

15 Popper KR. *Unended Quest: an Intellectual Autobiography*. Routledge, UK (2002).

16 Ferrari MJ, Bansal S, Meyers LA, Bjørnstad ON. Network frailty and the geometry of herd immunity. *Proc. Biol. Sci.* 273(1602), 2743–2748 (2006).

17 Bauch CT. Imitation dynamics predict vaccinating behaviour. *Proc. Biol. Sci.* 272(1573), 1669–1675 (2005).

18 Cojocaru MG, Bauch CT, Johnston MD. Dynamics of vaccination strategies via projected dynamical systems. *Bull. Math. Biol.* 69(5), 1453–1476 (2007).

19 Boëlle PY. Theoretical epidemiology and vaccine. *Rev. Med. Interne* 28(3), 161–165 (2007).

20 Kim SY, Goldie SJ. Cost–effectiveness analyses of vaccination programmes: a focused review of modelling approaches. *Pharmacoeconomics* 26(3), 191–215 (2008).

21 Pradas-Velasco R, Antoñanzas-Villar F, Martínez-Zárate MP. Dynamic modelling of infectious diseases: an application to the economic evaluation of influenza vaccination. *Pharmacoeconomics* 26(1), 45–56 (2008).

22 Szucs TD. Health economic research on vaccinations and immunisation practices – an introductory primer. *Vaccine* 23(17–18), 2095–2103 (2005).

23 Dawson A. Vaccination and the prevention problem. *Bioethics* 18(6), 515–530 (2004).

24 May T, Silverman RD. Free-riding, fairness and the rights of minority groups in exemption from mandatory childhood vaccination. *Hum. Vaccin.* 1(1), 12–15 (2005).

25 Calandrillo SP. Vanishing vaccinations: why are so many Americans opting out of vaccinating their children? *Univ. Mich. J. Law Reform* 37(2), 353–440 (2004).

26 Dawson A. What are the moral obligations of the traveller in relation to vaccination? *Travel. Med. Infect. Dis.* 5(2), 90–96 (2007).

27 Verweij MF, van den Hoven MA. Influenza vaccination in Dutch nursing homes: is tacit consent morally justified? *Med. Health Care Philos.* 8(1), 89–95 (2005).

28 Kahn J. What vaccination programs mean for research. *Am. J. Bioeth.* 7(3), 3–4 (2007).

29 Congeni BL. Vaccine shortages eliminate possibility for excess capacity in stockpiles. *Pediatr. Ann.* 33(9), 577–583 (2004).

30 McIntosh ED. Paediatric infections: prevention of transmission and disease – implications for adults. *Vaccine* 23(17–18), 2087–2089 (2005).

31 Elliott C, Farmer K. Immunization status of children under 7 years in the Vikas Nagar area, North India. *Child Care Health Dev.* 32(4), 415–421 (2006).

32 Menzies R, McIntyre P. Vaccine preventable diseases and vaccination policy for indigenous populations. *Epidemiol. Rev.* 28, 71–80 (2006).

33 Heymann DL, Aylward RB. Mass vaccination: when and why. *Curr. Top. Microbiol. Immunol.* 304, 1–16 (2006).

34 Garnett GP. Role of herd immunity in determining the effect of vaccines against sexually transmitted disease. *J. Infect. Dis.* 191(Suppl. 1), S97–S106 (2005).

35 Schellekens J, von König CH, Gardner P. Pertussis sources of infection and routes of transmission in the vaccination era. *Pediatr. Infect. Dis J.* 24(5 Suppl.), S19–S24 (2005).

36 Tan T, Halperin S, Cherry JD *et al.* Pertussis immunization in the global pertussis initiative North American region: recommended strategies and implementation considerations. *Pediatr. Infect. Dis. J.* 24(5 Suppl.), S83–S86 (2005).

37 Esen B, Coplu N, Kurtoglu D, Gozalan A, Akin L. Prevalence of high antibody titers of pertussis in Turkey: reflection of circulating microorganism and a threat to infants. *J. Clin. Lab. Anal.* 21(3), 154–161 (2007).

38 Lee GM, Murphy TV, Lett S *et al.* Cost effectiveness of pertussis vaccination in adults. *Am. J. Prev. Med.* 32(3), 186–193 (2007).

39 Casey JR, Pichichero ME. Acellular pertussis vaccine safety and efficacy in children, adolescents and adults. *Drugs* 65(10), 1367–1389 (2005).

40 Pichichero ME, Casey JR. Acellular pertussis vaccines for adolescents. *Pediatr. Infect. Dis. J.* 24(6 Suppl.), S117–S126 (2005).

41 Pósfay-Barbe KM. Whooping cough: a diagnosis one shouldn't forget. *Rev. Med. Suisse* 2(54), 503–506, 509–511 (2006).

42 Byrne S, Slack AT. Analysis of *Bordetella pertussis* pertactin and pertussis toxin types from Queensland, Australia, 1999–2003. *BMC Infect. Dis.* 6, 53 (2006).

43 Gomes MG, White LJ, Medley GF. The reinfection threshold. *J. Theor. Biol.* 235(2), 151–152 (2005).

44 Águas R, Gonçalves G, Gomes MGM. Pertussis: increasing disease as a consequence of reducing transmission. *Lancet Infect. Dis.* 6, 112–117 (2006).

45 Robbins JB, Schneerson R, Keith JM, Shiloach J, Miller M, Trollors B. The rise in pertussis cases urges replacement of chemically-inactivated with genetically-inactivated toxoid for DTP. *Vaccine* 25(15), 2811–2816 (2007).

46 Caro JJ, Getsios D, El-Hadi W, Payne K, O'Brien JA. Pertussis immunization of adolescents in the United States: an economic evaluation. *Pediatr. Infect. Dis. J.* 24(5 Suppl.), S75–S82 (2005).

47 Ali M, Emch M, Yunus M, Sack D *et al.* Vaccine protection of Bangladeshi infants and young children against cholera: implications for vaccine deployment and person-to-person transmission. *Pediatr. Infect. Dis. J.* 27(1), 33–37 (2008).

48 Longini IM Jr, Nizam A, Ali M, Yunus M, Shenvi N, Clemens JD. Controlling endemic cholera with oral vaccines. *PLoS Med.* 4(11), e336 (2007).

49 Sánchez J, Holmgren J. Virulence factors, pathogenesis and vaccine protection in cholera and ETEC diarrhea. *Curr. Opin. Immunol.* 17(4), 388–398 (2005).

50 Makwana N, Riordan FA. Bacterial meningitis: the impact of vaccination. *CNS Drugs* 21(5), 355–366 (2007).

51 Zhang Q, Finn A. Mucosal immunology of vaccines against pathogenic nasopharyngeal bacteria. *J. Clin. Pathol.* 57(10), 1015–1021 (2004).

52 Miranzi Sde S, Moraes SA, Freitas IC. Trends in *Haemophilus influenzae* type b meningitis in Brazil in children under five years of age from 1983 through 2002. *Rev. Soc. Bras. Med. Trop.* 39(5), 473–477 (2006).

53 Ladhani S, Slack MP, Heys M, White J, Ramsay ME. Fall in *Haemophilus influenzae* serotype b (Hib) disease following implementation of a booster campaign. *Arch. Dis. Child.* 93, 665–669 (2007).

54 Bauch CT, Anonychuk AM, Pham BZ, Gilca V, Duval B, Krahn MD. Cost–utility of universal hepatitis A vaccination in Canada. *Vaccine* 25(51), 8536–8548 (2007).

55 André FE. Universal mass vaccination against hepatitis A. *Curr. Top. Microbiol. Immunol*. 304, 95–114 (2006).

56 Lopez E, Debbag R, Coudeville L, Baron-Papillon F, Armoni J. The cost–effectiveness of universal vaccination of children against hepatitis A in Argentina: results of a dynamic health – economic analysis. *J. Gastroenterol*. 42(2), 152–160 (2007).

57 Genton B, D'Acremont V, Furrer HJ, Hatz C, Loutan L. Hepatitis A vaccines and the elderly. *Travel. Med. Infect. Dis.* 4(6), 303–312 (2006).

58 Hollinger FB, Bell B, Levy-Bruhl D, Shouval D, Wiersma S, Van Damme P. Hepatitis A and B vaccination and public health. *J. Viral. Hepat*. 14(Suppl. 1), 1–5 (2007).

59 Dagan R, Leventhal A, Anis E, Slater P, Ashur Y, Shouval D. Incidence of hepatitis A in Israel following universal immunization of toddlers. *JAMA* 294(2), 202–210 (2005).

60 Domínguez A, Oviedo M, Carmona G *et al.* Impact and effectiveness of a mass hepatitis A vaccination programme of preadolescents seven years after introduction. *Vaccine* 26(14), 1737–1741 (2008).

61 Wasley A, Fiore A, Bell BP. Hepatitis A in the era of vaccination. *Epidemiol. Rev.* 28, 101–111 (2006).

62 Van Effelterre TP, Zink TK, Hoet BJ, Hausdorff WP, Rosenthal P. A mathematical model of hepatitis a transmission in the United States indicates value of universal childhood immunization. *Clin. Infect. Dis*. 43(2), 158–164 (2006).

63 Armstrong GL, Billah K, Rein DB, Hicks KA, Wirth KE, Bell BP. The economics of routine childhood hepatitis A immunization in the United States: the impact of herd immunity. *Pediatrics* 119(1), e22–e29 (2007).

64 Rambout L, Hopkins L, Hutton B, Fergusson D. Prophylatic vaccination against human papillomavirus infection and disease in women: a systematic review of randomized controlled trials. *CMAJ* 177(5), 469–479 (2007).

65 Cutts FT, Franksceschi S, Goldie S *et al.* Human papillomavirus and HPV vaccines: a review. *Bull. WHO* 85(9), 719–716 (2007).

66 Lippman A, Boscoe M, Scurfield C. Do you approve of spending $300 million on HPV vaccination? No. *Can. Fam. Physician* 54, 175–177 (2008).

67 Regan DG, Philp DJ, Hocking JS, Law MG. Modelling the population-level impact of vaccination on the transmission of human papillomavirus type 16 in Australia. *Sex. Health* 4(3), 147–163 (2007).

68 Dasbach EJ, Elbasha EH, Insinga RP. Mathematical models for predicting the epidemiologic and economic impact of vaccination against human papillomavirus infection and disease. *Epidemiol. Rev.* 28, 88–100 (2006).

69 Chesson HW, Ekwueme DU, Saraiya M, Markowitz LE. Cost–effectiveness of human papillomavirus vaccination in the United States. *Emerg. Infect. Dis*. 14(2), 244–251 (2008).

70 Kulasingam S, Connelly L, Conway E *et al.* A cost-effectiveness analysis of adding a human papillomavirus vaccine to the Australian National Cervical Cancer Screening Program. *Sex. Health* 4(3), 165–175 (2007).

71 Piedra PA, Gaglani MJ, Kozinetz CA *et al.* Herd immunity in adults against influenza-related illnesses with use of the trivalent-live attenuated influenza vaccine (CAIV-T) in children. *Vaccine* 23(13), 1540–1548 (2005).

72 Piedra PA, Gaglani MJ, Kozinetz CA *et al.* Trivalent live attenuated intranasal influenza vaccine administered during the 2003–2004 influenza type A (H3N2) outbreak provided immediate, direct, and indirect protection in children. *Pediatrics* 120(3), e553–e564 (2007).

73 Schwartz B, Hinman A, Abramson J *et al.* Universal influenza vaccination in the United States: are we ready? Report of a meeting. *J. Infect. Dis*. 194(Suppl. 2), S147–S154 (2006).

74 Chantler T, Pace D, Wright A *et al.* Uptake and acceptability of influenza vaccination in day nursery children. *Community Pract.* 80(12), 32–36 (2007).

75 Wu JT, Riley S, Leung GM. Spatial considerations for the allocation of pre-pandemic influenza vaccination in the United States. *Proc. Biol. Sci*. 274(1627), 2811–2817 (2007).

76 Saffar MJ, Amiri-Alreza M, Baba-Mahmoodi F, Saffar H. Measles epidemiology in Mazandaran province, Iran, 2000–2002. *Trop. Doct.* 37(1), 30–32 (2007).

77 Rentsen T, Enkhtuya B, Nymadawa P *et al.* Measles outbreak after a post-honeymoon period in Mongolia, 2001. *Jpn. J. Infect. Dis*. 60(4), 198–199 (2007).

78 Hyde TB, Dayan GH, Langidrik JR *et al.* Measles outbreak in the Republic of the Marshall Islands, 2003. *Int. J. Epidemiol*. 35(2), 299–306 (2006).

79 Ong G, Hoon HB, Ong A, Chua LT, Kai CS, Tai GK. A 24-year review on the epidemiology and control of measles in Singapore, 1981–2004. *Southeast Asian J. Trop. Med. Public Health* 37(1), 96–101 (2006).

80 Friederichs V, Cameron JC, Robertson C. Impact of adverse publicity on MMR vaccine uptake: a population based analysis of vaccine uptake records for one million children, born 1987–2004. *Arch. Dis. Child*. 91(6), 465–468 (2006).

81 Wallinga J, Heijne JC, Kretzschmar M. A measles epidemic threshold in a highly vaccinated population. *PLoS Med*. 2(11), e316 (2005).

82 Girard MP, Preziosi MP, Aguado MT, Kieny MP. A review of vaccine research and development: meningococcal disease. *Vaccine* 24(22), 4692–4700 (2006).

83 Maiden MC, Ibarz-Pavón AB, Urwin R *et al.* Impact of meningococcal serogroup C conjugate vaccines on carriage and herd immunity. *J. Infect. Dis*. 197(5), 737–743 (2008).

84 Borrow R, Miller E. Long-term protection in children with meningococcal C conjugate vaccination: lessons learned. *Expert Rev. Vaccines* 5(6), 851–857 (2006).

85 Trotter CL, Gay NJ, Edmunds WJ. Dynamic models of meningococcal carriage, disease, and the impact of serogroup C conjugate vaccination. *Am. J. Epidemiol*. 162(1), 89–100 (2005).

86 Ortega-Sanchez IR, Meltzer MI, Shepard C *et al.* Active Bacterial Core Surveillance Team. Economics of an adolescent meningococcal conjugate vaccination catch-up campaign in the United States. *Clin. Infect. Dis*. 46(1), 1–13 (2008).

87 Caro JJ, Möller J, Getsios D *et al.* Invasive meningococcal disease epidemiology and control measures: a framework for evaluation. *BMC Public Health* 7(147), 130 (2007).

88 De Wals P, Coudeville L, Trottier P, Chevat C, Erickson LJ, Nguyen VH. Vaccinating adolescents against meningococcal disease in Canada: a cost–effectiveness analysis. *Vaccine* 25(29), 5433–5440 (2007).

89 Trotter CL, Edmunds WJ. Reassessing the cost–effectiveness of meningococcal serogroup C conjugate (MCC) vaccines using a transmission dynamic model. *Med. Decis. Making* 26(1), 38–47 (2006).

90 Hviid A, Rubin S, Mühlemann K. Mumps. *Lancet* 371(9616), 932–944 (2008).

91 Muhsen Kh, Aboudy Y, Mendelson E, Green MS, Cohen D. Prevalence of mumps antibodies in the Israeli population in relation to mumps vaccination policy and incidence of disease. *Epidemiol. Infect*. 136(5), 688–693 (2008).

92 Donaghy M, Cameron JC, Friederichs V. Increasing incidence of mumps in Scotland: options for reducing transmission. *J. Clin. Virol*. 35(2), 121–129 (2006).

93 Gijalva CG, Griffin MR. Population-based impact of routine infant immunization with pneumococcal conjugate vaccine in the USA. *Expert Rev. Vaccines* 7(1), 83–95 (2008).

94 Pebody RG, Leino T, Nohynek H, Hellenbrand W, Salmaso S, Ruutu P. Pneumococcal vaccination policy in Europe. *Euro. Surveill*. 10(9), 174–178 (2005).

95 Haber M, Barskey A, Baughman W *et al.* Herd immunity and pneumococcal conjugate vaccine: a quantitative model. *Vaccine* 25(29), 5390–5398 (2007).

96 Clarke SC, Jefferies JM, Smith AJ, McMenamin J, Mitchell TJ, Edwards GF. Potential impact of conjugate vaccine on the incidence of invasive pneumococcal disease among children in Scotland. *J. Clin. Microbiol.* 44(4), 1224–1228 (2006).

97 Claes C, Reinert RR, von der Schulenburg JM. Cost–effectiveness analysis of heptavalent pneumococcal conjugate vaccine in Germany considering herd immunity effects. *Eur. J. Health. Econ*. DOI: 10.1007/s10198-008-0098-1 (2008) (Epub ahead of print).

98 Isaacman DJ, Strutton DR, Kalpas EA *et al.* The impact of indirect (herd) protection on the cost-effectiveness of pneumococcal conjugate vaccine. *Clin. Ther*. 30(2), 341–357 (2008).

99 Lloyd A, Patel N, Scott DA, Runge C, Claes C, Rose M. Cost–effectiveness of heptavalent conjugate pneumococcal vaccine (Prevenar) in Germany: considering a high-risk population and herd immunity effects. *Eur. J. Health Econ*. 9(1), 7–15 (2008).

100 Hubben GA, Bos JM, Glynn DM, van der Ende A, van Alphen L, Postma MJ. Enhanced decision support for policy makers using a web interface to health-economic models – illustrated with a cost–effectiveness analysis of nation-wide infant vaccination with the 7-valent pneumococcal conjugate vaccine in The Netherlands. *Vaccine* 25(18), 3669–3678 (2007).

101 Beutels P, Thiry N, Van Damme P. Convincing or confusing? Economic evaluations of childhood pneumococcal conjugate vaccination – a review (2002–2006). *Vaccine* 25(8), 1355–1367 (2007).

102 Ray GT, Whitney CG, Fireman BH, Ciuryla V, Black SB. Cost–effectiveness of pneumococcal conjugate vaccine: evidence from the first 5 years of use in the United States incorporating herd effects. *Pediatr. Infect. Dis. J*. 25(6), 494–501 (2006).

103 McIntosh ED, Conway P, Willingham J, Hollingsworth R, Lloyd A. Pneumococcal pneumonia in the UK – how herd immunity affects the cost–effectiveness of 7-valent pneumococcal conjugate vaccine (PCV). *Vaccine* 23(14), 1739–1745 (2005).

104 Melegaro A, Edmunds WJ. Cost–effectiveness analysis of pneumococcal conjugate vaccination in England and Wales. *Vaccine* 22(31–32), 4203–4214 (2004).

105 Pletz MW, Maus U, Krug N, Welte T, Lode H. Pneumococcal vaccines: mechanism of action, impact on epidemiology and adaption of the species. *Int. J. Antimicrob. Agents* 32, 199–206 (2008).

106 O'Brien KL, Millar EV, Zell ER *et al.* Effect of pneumococcal conjugate vaccine on nasopharyngeal colonization among immunized and unimmunized children in a community-randomized trial. *J. Infect. Dis*. 196(8), 1211–1220 (2007).

107 Vila-Córcoles A. Advances in pneumococcal vaccines: what are the advantages for the elderly? *Drugs Aging* 24(10), 791–800 (2007).

108 Benninger MS. Acute bacterial rhinosinusitis and otitis media: changes in pathogenicity following widespread use of pneumococcal conjugate vaccine. *Otolaryngol. Head Neck Surg*. 138(3), 274–278 (2008).

109 Lipsitch M, O'Neill K, Cordy D *et al.* Strain characteristics of *Streptococcus pneumoniae* carriage and invasive disease isolates during a cluster-randomized clinical trial of the 7-valent pneumococcal conjugate vaccine. *J. Infect. Dis*. 196(8), 1221–1227 (2007).

110 Dagan R. The potential effect of widespread use of pneumococcal conjugate vaccines on the practice of pediatric otolaryngology: the case of acute otitis media. *Curr. Opin. Otolaryngol. Head Neck Surg.* 12(6), 488–494 (2004).

111 Adamkiewicz TV, Silk BJ, Howgate J *et al.* Effectiveness of the 7-valent pneumococcal conjugate vaccine in children with sickle cell disease in the first decade of life. *Pediatrics* 121(3), 562–569 (2008).

112 Tasslimi A, Wenger P, Pentakota SR, Brimacombe M, Burday M, Sinha A. Invasive pneumococcal disease in an underimmunized, high HIV prevalence population. *J. Infect*. 56(2), 99–102 (2008).

113 Fletcher MA, Laufer DS, McIntosh ED, Cimino C, Malinoski FJ. Controlling invasive pneumococcal disease: is vaccination of at-risk groups sufficient? *Int. J. Clin. Pract.* 60(4), 450–456 (2006).

114 Klugman KP, Madhi SA, Feldman C. HIV and pneumococcal disease. *Curr. Opin. Infect. Dis*. 20(1), 11–15 (2007).

115 Mackenzie G, Carapetis J, Leach AJ, Hare K, Morris P. Indirect effects of childhood pneumococcal vaccination on pneumococcal carriage among adults and older children in Australian Aboriginal communities. *Vaccine* 25(13), 2428–2433 (2007).

116 Käyhty H, Auranen K, Nohynek H, Dagan R, Mäkelä H. Nasopharyngeal colonization: a target for pneumococcal vaccination. *Expert Rev. Vaccines* 5(5), 651–667 (2006).

117 Metlay JP, Fishman NO, Joffe M, Edelstein PH. Impact of pediatric vaccination with pneumococcal conjugate vaccine on the risk of bacteremic pneumococcal pneumonia in adults. *Vaccine* 24(4), 468–475 (2006).

118 Centers for Disease Control and Prevention (CDC). Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease – United States, 1998–2003. *MMWR Morb. Mortal. Wkly Rep*. 54(36), 893–897 (2005).

119 Shafinoori S, Ginocchio CC, Greenberg AJ, Yeoman E, Cheddie M, Rubin LG. Impact of pneumococcal conjugate vaccine and the severity of winter influenza-like illnesses on invasive pneumococcal infections in children and adults. *Pediatr. Infect. Dis. J*. 24(1), 10–16 (2005).

120 McClure CA, Ford MW, Wilson JB, Aramini JJ. Pneumococcal conjugate vaccination in Canadian infants and children younger than five years of age: recommendations and expected benefits. *Can. J. Infect. Dis. Med. Microbiol*. 17(1), 19–26 (2006).

121 Black S, Shinefield H, Baxter R *et al.* Impact of the use of heptavalent pneumococcal conjugate vaccine on disease epidemiology in children and adults. *Vaccine* 24(Suppl. 2), S79–S80 (2006).

122 Poehling KA, Talbot TR, Griffin MR *et al.* Invasive pneumococcal disease among infants before and after introduction of pneumococcal conjugate vaccine. *JAMA* 295(14), 1668–1674 (2006).

123 Isaacman DJ, Fletcher MA, Fritzell B, Ciuryla V, Schranz J. Indirect effects associated with widespread vaccination of infants with heptavalent pneumococcal conjugate vaccine (PCV7; Prevnar). *Vaccine* 25(13), 2420–2427 (2007).

124 Watson M, Roche P, Bayley K *et al.* Laboratory surveillance of invasive pneumococcal disease in Australia, 2003 predicting the future impact of the universal childhood conjugate vaccine program. *Commun. Dis. Intell.* 28(4), 455–464 (2004).

125 Ho CF, Lin TY. Pneumococcal vaccines. *Chang. Gung. Med. J.* 28(11), 765–772 (2005).

126 Temime L, Dab W. Pneumococcal vaccination: expected benefits in adults. *Rev. Med. Interne* 28(1), 9–15 (2007).

127 Singleton RJ, Hennessy TW, Bulkow LR *et al.* Invasive pneumococcal disease caused by nonvaccine serotypes among Alaska native children with high levels of 7-valent pneumococcal conjugate vaccine coverage. *JAMA* 297(16), 1784–1792 (2007).

128 Dias R, Caniça M. Invasive pneumococcal disease in Portugal prior and after the introduction of pneumococcal heptavalent conjugate vaccine. *FEMS Immunol. Med. Microbiol.* 51, 25–42 (2007).

129 Iwai M, Takizawa T, Nakayama T *et al.* Evaluation of a two-dose administration of live oral poliovirus vaccine for wild and virulent vaccine-derived poliovirus type 1, 2, 3 strains in Japan. *Scand. J. Infect. Dis.* 40(3), 247–253 (2008).

130 Gidding HF, Backhouse JL, Gilbert GL, Burgess MA. National serosurvey of poliovirus immunity in Australia, 1996–1999. *Aust. NZ J. Public Health* 29(1), 48–52 (2005).

131 Frantzidou F, Diza E, Halkia D, Antoniadis A. A seroprevalence study of poliovirus antibody in the population of northern Greece. *Clin. Microbiol. Infect.* 11(1), 68–71 (2005).

132 Wang IJ, Huang LM, Chen HH, Hwang KC, Chen CJ. Seroprevalence of rubella infection after national immunization program in Taiwan: vaccination status and immigration impact. *J. Med. Virol.* 79(1), 97–103 (2007).

133 Huerta M, Davidovitch N, Ankol OE *et al.* Declining seroprevalence of rubella antibodies among young Israeli adults: a 12-year comparison. *Prev. Med.* 39(6), 1223–1226 (2004).

134 Dashraath P, Ong ES, Lee VJ. Seroepidemiology of varicella and the reliability of a self-reported history of varicella infection in Singapore military recruits. *Ann. Acad. Med. Singapore* 36(8), 636–641 (2007).

135 Marcitelli R, Bricks LF. Varicella zoster in children attending day care centers. *Clinics* 61(2), 147–152 (2006).

136 Marin M, Watson TL, Chaves SS *et al.* Varicella among adults: data from an active surveillance project, 1995–2005. *J. Infect. Dis.* 197(Suppl. 2), S94–S100 (2008).

137 Lopez AS, Guris D, Zimmerman L *et al.* One dose of varicella vaccine does not prevent school outbreaks: is it time for a second dose? *Pediatrics* 117(6), e1070–e1077 (2006).

138 Quian J, Rüttimann R, Romero C *et al.* Impact of universal varicella vaccination of one year-olds in Uruguay: 1997–2005. *Arch. Dis. Child.* 93, 845–850 (2008).

139 Heininger U, Seward JF. Varicella. *Lancet* 368(9544), 1365–1376 (2006).

140 Nardone A, de Ory F, Carton M *et al.* The comparative sero-epidemiology of varicella zoster virus in 11 countries in the European region. *Vaccine* 25(45), 7866–7872 (2007).

141 Gonçalves G. Incerteza e Riscos em Epidemiologia e Saúde Pública. In: *Encontro de Saberes. Três Gerações de Bolseiros da Gulbenkian*. Tostões A, Arantes e Oliveira ER, Paixão JMP, Magalhães P (Eds). Fundação Calouste Gulbenkian, Lisbon, Portugal 455–471 (2006).

142 Last JM. Epidemiology and public health. In: *Teaching Epidemiology. A Guide for Teachers in Epidemiology, Public Health and Clinical Medicine (2nd Edition).* Olsen J, Saracci R, Trichopoulos D (Eds). Oxford University Press, Oxford, UK, 21–32 (2001).

Website

201 ECDC. Guidance for the introduction of HPV vaccines in EU countries. Guidance Report. Stockholm, January 2008 http://www.ecdc.europa.eu/pdf/HPV_report.pdf

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