Herd Immunity/Protection: an Important Indirect Benefit of Vaccination

“Les Pensières”
Fondation Mérieux Conference Centre
Veyrier-du-Lac - France
October 25-27, 2010

Steering Committee:
• Marie-Claude BONNET
• John CLEMENS
• Catherine DUTEL
• Jacques LOUIS
• Peter SMITH

Coordination:
• Katia MIELCZAREK
Welcome Letter

October 25, 2010

Dear Participant,

It is our pleasure to welcome you to the symposium entitled:

“Herd Immunity/Protection: an Important Indirect Benefit of Vaccination”

in Fondation Mérieux’s Conference Centre “Les Pensières.” We hope you will enjoy this meeting, which brings together some of the world’s foremost experts.

The format of the discussion is intended to generate discussion and interaction among participants and to foster the dissemination of new information on this topic. The conference will provide an opportunity for specialists to exchange their knowledge and experience through collaboration with researchers from around the world.

Over the next three days, the team at Les Pensières will be on hand to help you with any questions you may have and to make your stay and conference as comfortable and valuable as possible.

Benoît Miribel
Director General
Fondation Mérieux

For more information: www.fondation-merieux.org
One of the aims of this conference is to share cross-functional knowledge and to increase awareness of the diverse range of benefits that result from successful vaccination programs with a specific focus on herd immunity / protection.

Vaccination is a very powerful public health tool for preventing many infectious diseases. In addition to the well-documented direct benefit to the vaccinated individual there are multiple indirect benefits to the close contacts, neighbors, and at the community level as well as for society as a whole. It is well known that not everyone in a population needs to be immunized to eliminate disease, because successful immunization has an effect on the transmission of disease. How can we define this benefit? How can we measure it? What are the different methodologies?

The economic impact of vaccination is a rare example of a health intervention that can be not only cost beneficial but also cost saving. Herd immunity / protection are very relevant factors to consider before introducing a new vaccine in an immunization programme and are also very important for monitoring and assessing / evaluating this programme.

The indirect benefit of vaccination should also be considered in the context of diverse cultural, epidemiological, socio-economical, climatic and geographical as well as political situations in different areas of the world. This will be illustrated with different case studies for different diseases in different contexts.

In addition, animal vaccination should also be considered when evaluating the overall benefit of vaccination to human public health.

This conference will bring together vaccinologists, epidemiologists, immunologists, veterinarians, health economists, representatives from regulatory agencies and from non governmental organizations,
### Scientific Programme

**Monday 25 October 2010**

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**Herd immunity/protection: general concept and methodological approaches to measurement**  
Chaired by Jacob John

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**11.40 - 16.30**  
**General approaches to infectious diseases modelling**  
Chaired by Daniel Levy-Bruhl

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### Session 3  
**16.30 - 18.30**  
**Herd immunity/protection: case studies**  
Chaired by Marie-Claude Bonnet & Kim Mulholland

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12.20 - 14.00  Lunch

Session 5
14.00 - 15.30  An example of herd effect in the context of non-vaccine interventions
Chaired by Peter Smith

14.00 - 14.20  Achieving herd effects through non-vaccine interventions  Simon BROOKER
14.20 - 14.40  Discussion
14.40 - 15.00  Conclusions and end of the meeting
15.00 - 15.15  Coffee before departure
Session 1

Herd immunity/protection: general concept and methodological approaches to measurement
Concepts of herd immunity and protection

Peter SMITH
London School of Hygiene and Tropical Medicine - UK

Herd protection is generally discussed in the context of vaccines, but the concept has wider applicability. The term is used when intervention measures applied to individuals have a greater effect at a population (herd) level than simply the sum of the effects on the individuals to which the intervention is applied. Most vaccines are designed primarily to protect vaccinated individuals against the target infection. However, in addition to this direct effect of vaccination, vaccination may increase the level of population (or herd) immunity by increasing the proportion of the population who are immune from infection. For infections that are transmitted from person-to-person, or for which humans are an important reservoir, increased herd immunity may result in a lower risk of infection among unvaccinated persons. This is called an indirect effect of vaccination. The effect of vaccination in increasing herd immunity is important to take into account when evaluating the cost-effectiveness of vaccination programmes. It is also important in planning disease elimination programmes as this state may be achieved without having to vaccinate the entire population. An example will be given of how the indirect effect of vaccination operates and the implications this has both disease control programmes and the interpretation of vaccine trials.
Ethical perspective on herd immunity

Jacob JOHN
Christian Medical College - India

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Concept and methodological approaches to measure herd protection in individually randomized trials

Mohammad ALI
International Vaccine Institute - Korea

Background: Vaccine herd protection results from the reduction of the intensity of transmission of the targeted infection in a population, owing to the presence of persons made immune to the infection by vaccination. This reduced intensity of transmission stems from the reduced ability of exposed vaccines to transmit the infection to their subsequent contacts. The ability to confer herd protection may be crucial to policy deliberations for introduction of the vaccines that are expensive and direct protection is moderate in magnitude. Traditionally, herd protection has been evaluated using cluster randomized trials. New methodological developments now afford the possibility of evaluating herd protection in individually randomized trials.

Methods: In individually randomized trials, there may be differences in vaccine coverage in clusters of the target population due to chance variations in randomized assignments and to different rates of eligibility and participation. If suitable clusters can be identified and if there is sufficient variation in vaccine coverage between these clusters, vaccine herd effects can be assessed by evaluating the correlation of disease incidence with levels of vaccine coverage in these clusters. With this logic, an inverse relationship between the incidence of the target disease among non-vaccinees and the level of vaccination coverage of the cluster would indicate indirect protective effects. Similarly, an inverse relationship between the incidence of the target disease among vaccinees and the level of vaccine coverage of the cluster would reflect total vaccine protection. This approach was recently used in a reanalysis of the 1985 trial of killed oral cholera vaccines in Bangladesh, which was a placebo-controlled and individually randomized trial. The 1985 Bangladesh trial evaluated a cholera toxin B subunit-killed whole cell vaccine.

Results: The study population, totaling 89,596 persons, resided in 6,423 baris, patrilineally linked groups of houses. The baris of the study area are known to be the geographic unit of transmission of Vibrio cholerae 01, and were selected as clusters for the analysis. Since it is a non-random, non-blinded comparison of the clusters, and that were selected post hoc, a multi-variable model was employed in the analysis to adjust for potential confounders. The analysis found significant inverse relationships between vaccine coverage of the baris and the incidence of cholera in recipients of both placebo and vaccine, reflecting indirect and total protection, respectively.
Substantial herd protection of infants and young children was observed with modest levels of vaccine coverage of adult women.

**Conclusion:** The methodological issues in the analysis permit estimation of vaccine herd protective effects in individually randomized trials, which are conventionally used as designs for pre-licensure trials. Assessment of herd protection is important to evaluate cost-effectiveness of vaccines and may support decisions in implementing vaccines for wider public health use.
Cluster-Randomised Trials of Vaccines to Estimate Vaccine Herd Protection

John CLEMENS
International Vaccine Institute - Korea

Criteria for introducing new vaccines into routine public health practice are becoming increasingly stringent. For vaccines that are expensive and confer moderate levels of individual protective efficacy, the ability to confer herd protection may be crucial to policy deliberations about vaccine introduction. Traditionally, vaccine herd protection has been evaluated after a vaccine is introduced, delaying the use of data on herd effects to inform decisions about vaccine introduction. New methodological developments now afford the possibility of evaluating herd protection before introduction of a vaccine into public health programs. One approach is the cluster-randomised trial, a design in which clusters of individuals rather than individuals per se serve as the units of randomisation. If clusters for these trials meet several conditions, these trials can estimate in an unbiased fashion the measures conventionally used to characterize vaccine herd protection: indirect protection, total protection, and overall protection. Although these trials do not replace the need for individually randomized trials in the clinical development of vaccines, they can provide an early “read-out” on whether a vaccine is capable of conferring herd protection and may thus accelerate policy decisions to use a vaccine in public health programs.
Session 2

General approaches to infectious diseases modelling
Approaches and examples of modelling herd immunity/protection

Ira LONGINI
Hutchinson Research Center & University of Washington - USA

In this talk, I present methods and study designs for estimating the direct, indirect, total and overall effectiveness of vaccines studies. I will describe study designs on different scales ranging from household studies, i.e., mini cohort studies, to those involving entire communities. This will include a discussion of how to use the proper comparison groups and the role of randomization. I will illustrate these methods in a description of a past analysis of cholera vaccines and past, ongoing and planned vaccine trials for influenza. I will put these studies in the context of cluster randomized and step-wedge designs.
Examples of vaccines where mathematical modelling was used as a tool for decision making

Daniel LEVY-BRUCH
National Institute for Public Health Surveillance - France

The decision of introduction of a new vaccine in the immunisation schedule is a complex and multidisciplinary process based on the assessment of the risk-benefit balance and, increasingly, on the assessment of the cost-effectiveness ratio of the vaccination. This decision relies on mathematical models allowing anticipating the indirect effects of a mass vaccination on the epidemiology of the target disease, which are often beneficial but can also be detrimental. Some instances where the anticipated herd immunity effects of a new vaccination have been a main determinant of the decision, either positive or negative, will be presented.
The benefits and limits of modelling infectious diseases

Deirdre HOLLINGSWORTH
Imperial College - UK
Recent developments in vaccine development and financing have rapidly expanded the vaccine market for developing countries. The availability of these new vaccines presents policy makers in developing countries with difficult decisions regarding how to expend limited financial resources. This presentation examines new models that incorporate private willingness to pay for vaccines and mathematical models of cholera vaccine protection to aid policy development in resource-limited developing countries. The rural Matlab, Bangladesh area is used as a case study to illustrate the models. This site is unique in that recent studies have evaluated 1) the vaccine coverage-herd protection relationship, 2) private willingness to pay for cholera vaccines, and 3) the public and private costs of cholera illness. These data are incorporated into cost benefit and cost effectiveness models to optimize potential vaccination programs assuming fixed budget constraints. These optimization models can examine the potential for cross-subsidies to improve program efficiency both in consideration of social net benefits and in consideration of health impacts based on the number of disability adjusted life years (DALYs) saved given similar budget constraints.

Specifically, I split the population into four subgroups: 1) adults in average incidence villages, 2) children in average incidence villages, 3) adults in high incidence villages and 4) children in high incidence villages. These models can then be solved for a set of four user fees that would maximize either net societal benefits or total DALYs averted given net revenue constraints. I examined a number of different pricing models for vaccination programs. These include simple models in which all four groups are charged the same price and optimized models in which different subgroups are charged different prices. The optimal prices that maximize net societal benefits tend to fall within tightly bound ranges around the marginal cost of vaccination. As a result, the prices for each of the four groups would typically fall within US$1 of one another when societal net benefits are maximized. This occurs because the private willingness to pay for vaccination was not significantly different in high-incidence villages relative to average incidence villages. Since willingness to pay functions drive the calculation of direct and indirect benefits, the differences in optimal prices result solely from small differences in herd protection effects and public COI savings across population subgroups. However, public COI savings tend to be small relative to direct and indirect benefits.
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Program outcomes are similar for models that maximize the number of DALYs averted relative to budget constraints. Relative to net benefit maximization models, the optimal prices derived by the DALY optimization models have more variability across subgroups. The optimal prices for groups with high incidence tend to be smaller (i.e., for children relative to adults and for high incidence villages relative to average incidence villages). As a result, predicted coverage rates at optimal prices are greater for higher incidence groups. However, the population average coverage rates remain about the same, leading to similar levels of herd protection for unvaccinated persons across the two models. As a result, there are very small differences in the numbers of DALYs saved for the net benefit maximization model versus the DALY maximization model, despite the differences in optimal prices. Monte Carlo Simulation results indicate that the differences in net societal benefits or DALYs saved for the two types of models are less than 10% across a range of 500 independent parameter draws.

The uncertainty in optimal pricing is driven primarily by uncertainty in the fixed and variable costs of vaccination programs. If program costs are greater than expected, it would be necessary to charge all subgroups higher prices in order to maintain revenue neutrality. When higher prices are charged, coverage rates decline, herd protection effects are diminished, and fewer cholera cases are avoided. Thus, variation in societal net benefits and DALYs are also strongly impacted by uncertainty in program costs. Uncertainty in net societal benefits is also driven by uncertainty in demand function parameters. If demand is greater than expected, net societal benefits increase because cholera protection is perceived to be more valuable to the community. The uncertainty in DALYs saved is primarily driven by variability in case fatality and incidence rates, such that more DALYs are saved when incidence and case fatality rates are greater. It is believed that cholera case fatality rates may be lower in Matlab relative to other rural communities because Matlab’s hospital is able to provide high quality treatment.

The cost per DALY saved varies depending on the coverage rate of the program. The average cost per DALY is minimized at modest coverage rates (20-40%). At higher coverage rates, the cost per DALY saved would be higher due to diminishing returns to scale of herd protection. At very low coverage rates, the average cost per vaccination is high because it is assumed that fixed costs are accrued to initiate the program regardless of coverage rate. This analysis is most relevant for vaccines that provide short term protection and generate herd protection effects against diseases that may strike any age group (e.g., cholera, typhoid, and influenza). For these vaccines, it is especially important to target high-risk groups, but also to target groups that may have a disproportionate impact on herd protection. Future research on the herd protection effects of vaccination should assist in improving the efficiency of targeted vaccination campaigns. This analysis also shows that herd protection effects greatly improve the economic attractiveness of vaccination programs and that substantial gains in public health may be achieved via modest vaccine coverage rates.
Session 3

Herd immunity/protection: case studies
Herd immunity/protection case studies: Hib vaccines

Richard ADEGBOLA
Bill & Melinda Gates Foundation - USA

Conjugation of Hib polysaccharide to immunogenic proteins can confer important new characteristics on Hib vaccines. They become immunogenic in young children aged less than 18 months, who are the primary risk group for Hib disease, induce immunological memory and have protective effect on nasopharyngeal carriage leading to a reduction in transmission and herd protection among unvaccinated persons. In The Gambia, Hib disease was eliminated in the community at a point when only 41% of potential cases would have been protected by the direct effects of immunization, based on a documentation of less than optimal vaccination coverage with 3 doses of only 68%. Two doses were required for the direct protection of children but most received their second dose too late to benefit from direct protection. The remainder was attributed to indirect effects resulting from a dramatic reduction in carriage of Hib. In Malawi decreases in incidence of Hib meningitis were recorded among children too old to have received vaccination. Additional benefits from herd protection can make Hib vaccine to be more effective than is suggested by an efficacy trial.
Herd immunity and pneumococcal vaccines

Kim MULHOLLAND
London School of Hygiene and Tropical Medicine - UK

Before pneumococcal vaccines became available in 2000 there was considerable debate about whether or not they would produce a significant herd effect. Even the most optimistic did not predict the impact that has been seen in the USA where the impact on herd immunity in older children and adults has more than doubled the beneficial effects of the vaccine. This has taught us a great deal about the epidemiology of pneumococcal disease in the USA. The extent of the herd immunity effect demonstrates that transmission is mainly vertical, from young child to adult, such that reduction of carriage in a young child leads directly to reduced disease in the child’s adult contacts. This is due to the vaccine’s profound impact on pneumococcal carriage. Unfortunately the same effect on carriage is responsible for shifts in the circulating serotypes, such that vaccine serotypes come to be replaced by non-vaccine serotypes. This has lead to an increase in disease due to non-vaccine serotypes and a diminution in the effectiveness of the vaccine. Thus, the indirect effect of pneumococcal vaccine can be seen as both positive (herd immunity) and negative (serotype replacement). In different settings, where the underlying epidemiology may differ, the balance between these effects leads to different trends in pneumococcal disease rates.
How much infant pertussis is prevented by a preschool booster?

Anders HVIID
Statem Serum Institute - Denmark

Infants are a group of particular interest in pertussis epidemiology. Pertussis among infants can be severe and given current immunization schedules infants are either unvaccinated or only partially vaccinated. Boosting immunity in childhood, adolescence and throughout adulthood has been proposed to improve pertussis control by directly decreasing rates of infection in booster vaccinated populations and indirectly by increasing herd immunity in susceptible populations such as infants. We developed a novel approach to measuring the impact of a preschool booster on pertussis in infants. Our approach used the Danish nationwide demography and health registers to construct household histories detailing the number and ages of adults and other children living at the same address as the cohort infants. We then estimated the risk of pertussis according to different household histories. Based on these risks and according to different assumptions about the effectiveness of a preschool booster, we were able to estimate the possible impact on infant pertussis. We estimated the proportion of preventable infant pertussis to be in the range of 7-33%, varying according to age at booster vaccination, uptake and how effective the booster prevents transmission of pertussis.
Hepatitis A vaccines

Ron DAGAN
Soroka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva - Israel

Hepatitis A is fast increasing in regions which are in transition from high to intermediate endemicity. This is accompanied with often severe outbreaks. The main reason for such dynamics can be attributed to improving hygiene, resulting in older age of exposure to HAV on the one hand (resulting in higher rate of symptomatic cases despite decreased infection rate), and on the other hand, unlike non-endemic region, still high circulation of the HAV.

As a consequence, the WHO recommended universal mass childhood vaccination in countries with intermediate endemicity. Several approaches will be reviewed, all resulting in marked herd immunity derived from the fact that vaccinated subjects (mostly young children) do not disseminate anymore HAV through stool in the asymptomatic cases, preventing both human-to-human transmission and water contamination.

In Spain (Catalonia), vaccinating adolescents resulted in reduction of disease in all ages. In the US, despite only partial vaccination of children in the 17 high-risk states, the disease is close to being eliminated nationwide. In Australia, vaccinating Aborigenes < 5 years old resulted in the near disappearance of disease in the entire population. In Puglia, Italy, vaccinating toddlers and adolescents reduced disease in all ages and prevented foodborne outbreaks, which caused damage to tourism. In Israel, toddler-only nationwide programs caused 99% reduction of disease within 3 years. In Argentina, a one-dose only regimen HAV vaccine has been given to toddlers since 2006, resulting in what appears to be close to 90% disappearance of the disease in all ages, and the total disappearance of fulminant hepatitis cases.

Therefore, post vaccination HAV epidemiology may be the one of the easiest ways to demonstrate herd immunity in vaccinology.
Dengue vaccines

Derek CUMMINGS
John Hopkins School of Public Health - USA

The four antigenically distinct serotypes of dengue are a major cause of morbidity and mortality worldwide. Multiple vaccine candidates are currently in development, with one candidate undergoing phase 2B evaluation. Pre-existing immunity to one of the dengue serotypes is a strong risk factor for severe disease upon infection with a heterologous serotype. The mechanism of this increased severity is either immune mediated increased viremia of secondary infections or immune mediated increase pathogenicity in the absence of enhanced infection. In both these cases, there is substantial concern that imperfect vaccines could give rise to increased severity of illness among some vaccine recipients. Using transmission models, I present projections of the impact of a dengue vaccine under multiple hypotheses of how a dengue vaccine might work. The models are useful in identifying vaccines that place populations at increased risk, periods of time after the initiation of a vaccine campaign where increased cases might be observed and optimal immunization campaigns with respect to age.
Benefits from herd immunity: Rabies vaccination of pets and wildlife

Katharina D.C. STÄRK SPALLEK
Royal Veterinary College - UK and SAFOSO - Switzerland

Despite global efforts to control rabies in animals, it is still considered a "neglected zoo-nosis" by the WHO. Rabies was estimated to be responsible for 55,000 human deaths and the loss of 1.74 million disability-adjusted life years in Asia and Africa (Knobel et al., 2005). Rabies vaccination provides benefits both for the individual animal and for the whole population. For the individual animal, benefits from rabies vaccination include protection against infection and diseases as well as – in the case of pet animals – free movement between countries with no or minimal quarantine. Vaccination campaigns have successfully eradicated rabies from populations, regions and countries thus providing direct health benefits for all susceptible animals and humans.

However, rabies remains a considerable problem in many areas of the world where it is endemic not only in wildlife but also in pets, particularly stray dogs. Various dog vaccination strategies have been evaluated in Asia and Africa, indicating that dog vaccination is logistically feasible and affordable provided that flexible designs and delivery methods are used that match the local settings. Wildlife reservoirs such as foxes (Vulpes vulpes), coyotes (Canis latrans), raccoons (Procyon lotor), raccoon dogs (Nyctereutes procyonoides) and skunks (Mephitis mephitis and other species) have also been targeted by immunization campaigns. Vaccine efficacy, vaccination tactics (oral vs. injection), baiting and trapping methods as well as delivery logistics are all important success factors. Vaccination coverage of 70% is considered to be effective to provide herd immunity that prevents outbreaks and eliminates disease (Kaare et al., 2009).

As case examples, wildlife and stray dog rabies vaccination illustrate the direct and indirect population-level benefits. Economic and epidemiological analyses are important tools to optimize vaccination strategies and tactics as well as to assure cost-effectiveness of a campaign. Direct and indirect benefits must be included in the over-all evaluation of a campaign. In the case of rabies, economic assessments have mainly included direct cost savings due to a reduced need for management of rabies cases, the reduced need of rabies testing of animals and reduced compensation payments for animals that had to be destroyed because of rabies (Sterner et al., 2009). Indirect benefits include public health benefits but also impacts on food security as a consequence of reduced losses related to rabies in livestock. Because rabies is a zoonotic disease, vaccination does benefit both animal and public health. Evaluation of rabies vaccination must therefore include benefits across susceptible populations. Additionally, prevention of rabies also provides benefits to animal welfare and conservation.
Session 4

Herd immunity and decision making
A WHO perspective

Ana Maria HENAO-RESTREPO
WHO - Switzerland

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Adonor perspective: GAVI

Jon PEARMAN
GAVI - France

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Session 5

An example of herd effect in the context of non-vaccine interventions
Achieving herd effects through non-vaccine interventions

Simon BROOKER
London School of Hygiene and Tropical Medicine - UK

Similar to how vaccination can lower the risk of infection among unvaccinated persons, certain disease control interventions can have beneficial effects for individuals who have not received the intervention. The effects are most commonly observed for parasitic diseases whereby the intervention serves to reduce sources of infection. Examples will be presented for interventions against malaria and human helminth infections. The strength of observed community-wide effects is determined by the underlying transmission dynamics and spatial dependency. Failure to account for community-wide effects (also known as externalities) can lead to underestimating the impact of disease control programmes.
Speakers

Richard ADEGBOLA
Bill & Melinda Gates Foundation
USA

Mohammad ALI
International Vaccine Institute
Korea

Marie-Claude BONNET
Sanofi Pasteur
France

Simon BROOKER
Kenya Medical Research Institute
Kenya

John CLEMENS
International Vaccine Institute
Korea

Derek CUMMINGS
John Hopkins School of Public Health
USA

Ron DAGAN
Ben-Gurion University
Israel

Paul FINE
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