Perspectives on Benefit-Risk Decision-making in Vaccinology

"Les Pensières"
Fondation Mérieux Conference Center
Veyrier-du-Lac - France
23-25 June 2014

Steering Committee:
• Michael GREENBERG
• Corinne JOUQUELET-ROYER
• Jacques LOUIS
• Lydie MARCELON
• François SIMONDON

*Cindy Grasso meeting Coordinator

des racines pour la vie • roots for life
Welcome letter

Dear Participant,

It is our pleasure to welcome you to the symposium:

"Perspectives on Benefit-Risk Decision-making in Vaccinology"

in Fondation Mérieux’s Conference Center, "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.

Yours sincerely,

Benoît Miribel

Director General
Fondation Mérieux
Regulators historically have made approval decisions on medicinal products, including vaccines, based on quality, safety, and efficacy. Today, these decisions are increasingly being based on the balance between benefit and risk to individuals and public health. The core task of regulatory agencies is to weigh the probable benefit to health of a pharmaceutical product or technology against any probability of risk, injury or illness arising from its use. Benefit-Risk (B-R) assessments have classically been based on expert opinion. There is increased attention and research on more structured approaches to making B-R assessments, and to monitoring their evolution over time. B-R assessments are thus an essential part of the overall assessment of a medicinal product throughout its development and life cycle. Advisory bodies are also moving in this direction and frameworks for such evaluations are described, such as the one adopted by the US Advisory Committee on Immunization Practices (ACIP) and by the Robert Koch Institute (RKI) in Germany.

A number of methods allow the comparison of only one benefit and one risk indicator. These evaluations have been mostly focused on pharmaceuticals and little attention has been given to their application to vaccines. In the particular case of vaccines, as opposed to medicines or medical devices, additional factors may need to be taken into consideration when assessing benefit-risk, such as the additional potential population benefit afforded through herd immunity. European regulatory agencies do not currently recommend specific qualitative or quantitative benefit-risk methods. However, some are being used such as the PrOACT-URL framework for the EMA’s recent Benefit-Risk Assessment Methodology project. EMA encourages further exploration of the more quantitative multi-criteria decision analysis (MCDA) to aid benefit-risk decision-making and considers MCDA as a strong candidate for testing in a regulatory setting.

The U.S. Centers for Disease Control and Prevention (CDC) currently makes recommendations using the ACIP Framework, and FDA recommended certain qualitative methods in 2013. Initiatives are on-going that involve regulators, industry and academia to assess existing qualitative and quantitative methodologies and come to a consensus. Benefit-risk can be viewed from multiple perspectives, including that of the individual or of Society. As such, there are important ethical considerations which should be integrated when deciding how to assign weight to the various benefits and risks, as well as how to balance individual vs. societal needs and expectations. Furthermore, the data needed for initial B/R monitoring has not yet been defined. The purpose of this seminar is to bring together experts and interested individuals from diverse disciplines to:

1. Explore, through examples, the specificities of benefit-risk evaluation of vaccines according to different perspectives;
2. Discuss data needed and methodologies for benefit-risk analysis in vaccine development and in post-marketing surveillance of vaccination programs, in terms of respective contributions, complementarities, limitations.
3. Draw upon the two points above to recommend ways to maximize the B/R of vaccines and vaccination programs.
## Scientific programme

### Monday 23 June 2014

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### Tuesday 24 June 2014

**Session 1**

**Methodologies for Assessing Benefits/Risks of Vaccines**

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**Session 2**

**Case studies of Benefit Risk of Vaccines (with historical examples)**

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<td>The Rationale and Evidence Base Supporting the Vaccination of Frail/Elderly Rather than the «Transmitters» (Children/Young Adults) in Most Countries</td>
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<td>Umesh D. PARASHAR</td>
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<td>Polio (Benefit/Risk as a Function of Time; OPV vs IPV)</td>
<td>Joel CALMET</td>
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<td>Vaccination of Pregnant Women: Benefits/Risks Assessment</td>
<td>Carol BAKER</td>
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<td>Data Needed for Benefits/Risks Assessment of Vaccines</td>
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<td>Benefit-Risk assessment of vaccines, the perspective of a European regulatory agency</td>
<td>Christoph CONRAD</td>
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<td>Perpectives and Expectations on Benefits/Risks Assessment of Vaccines: the US View</td>
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<td>An Industry Perspectives and Expectations on Benefits /Risks Assessment of Vaccines</td>
<td>Alena KHROMAVA</td>
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Scientific programme

Session 4

**Beyond Benefits/Risks Assessment: Ethics/Choice/Decision making**

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<td>Vaccine Acceptance or Refusal: Individual Choice vs Societal Needs</td>
<td>Heidi LARSON</td>
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<td>Company B/R Decision making Process of Vaccines from Early Development to Post Marketing Experience</td>
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<td>Social Communication about Vaccines: from Conventional Media to Communication</td>
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<td>Ethical Analyses of Measures to Increase Vaccination Rates</td>
<td>Claudia EMERSON</td>
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<td>Decision-Making Framework of the German Standing Committee on Vaccination (STIKO)</td>
<td>Ole WICHMANN</td>
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Vaccine preventible diseases are sadly on the rise in many parts of the world. Parents of school-age children are increasingly claiming nonmedical exemptions to refuse vaccinations. The resultant unvaccinated pockets in many areas of the world have been linked with outbreaks of vaccine-preventable diseases including mumps, measles, pertussis and flu. Other vaccines for shingles and HPV have had very poor uptake. Booster rates are poor. Even health care professionals and workers have poor rates of vaccination. Awareness of the facts alone do not seem to change vaccination behavior. What can and should be done about these huge public health challenges?
Session 1
Methodologies for Assessing Benefits/Risks of Vaccines
A Quantitative Approach for Assessment of Benefit/Risk of Vaccines

Filip MUSSEN, PhD
Janssen R&D, Pharmaceutical Companies of Johnson & Johnson

Whilst benefit-risk appraisals of medicines and vaccines are the cornerstone of regulatory approval processes since more than 50 years, systematic approaches and methodologies for benefit-risk evaluation are rather new and very few well-accepted models exist today, if any. As a prerequisite for any discussion on benefit-risk methodology, it is important to establish a number of key definitions and concepts, including terms such as ‘benefits,’ ‘risks’ and ‘quantitative’ models. Equally important will be to explore where in the development and life-cycle of vaccines systematic benefit-risk approaches could provide value. In addition, the operational characteristics of qualitative and quantitative approaches will be defined, and the challenges and the outstanding issues for applying such methods will be outlined specifically as they relate to vaccines. Those include capturing value judgments and incorporating these into an overall benefit-risk appraisal, and dealing with uncertainty. As most stakeholders believe today in the need for a toolbox of benefit-risk methods, it will be demonstrated how quantitative approaches complement more qualitative approaches, also called benefit-risk frameworks. The importance of upstream activities such as collecting adequate efficacy and safety data sets, and downstream activities such as the communication of benefit-risk decisions will be considered. Finally, an important emerging field are the so-called patient-centred benefit-risk approaches, such as patient preference studies.

In this presentation, the history of benefit-risk methodology will be summarized and a status update on this emerging field will be provided. The perspectives of different stakeholders on the use of systematic benefit-risk approaches including those of Health Authorities will be summarized.
Lesson Learnt from IMI-PROTECT Project in Benefit-Risk Assessment of Medications, and Adaptation to Vaccines

Shahrul MT-ISA
School of Public Health, Imperial College London

The IMI-PROTECT members have advanced the understanding of both the integration and visual representation of benefit and risk data. Following a robust review of the literature, selected methodologies and visualisation techniques were applied in several case studies, each one constructed from publicly available data and representative of the more challenging benefit-risk assessments encountered throughout the lifecycle of a drug. The results of this work confirmed the added value of using more formal and structured approaches to the benefit-risk assessment of medicines to improve the transparency and communicability of this process. The experience of the case study teams has been distilled into a clear set of practical recommendations for benefit-risk decision processes and supporting tools, and these are organised around the five stages of a generic benefit-risk assessment roadmap to aid the selection of methodologies.

In particular, stakeholders may have different perspectives on benefit and risk criteria, and these perspectives should be made explicit upfront. Perhaps more important than drugs, in vaccines, the benefit-risk assessment should consider who the decision-maker is, who the decision is to be made for, and any other stakeholders involved. In the situation where multiple stakeholders exist, care should be taken so that the conflicting perspectives would not interfere with the framing of the decision problem; especially when individual and population benefit-risk balance are the two competing sides of the same coin. Methodologies that deal directly with stakeholder perspectives may offer an “all-inclusive” solution, but in practice not a single methodology can fully capture all aspects of a benefit-risk assessment. Methodology choices should match the complexity of the problem. The aims of this presentation are (i) to provide a toolkit for selection of benefit-risk methodologies, (ii) to demonstrate the added value of quantitative integrative benefit-risk methodologies, and (iii) to demonstrate effects of varying stakeholder perspective.
Critical Choices to be Made in Benefits/Risks Assessments of Vaccines: Challenges in Performing a Quantitative BR Assessment for Vaccines

Thomas VERSTRAETEN, MD, MSc
P95

Whereas there is still hesitancy on the use of quantitative approaches for assessing the benefit-risk (BR) balance of pharmaceuticals, there is a growing body of experience brought in the public domain, not the least by the PROTECT consortium. The newly created ADVANCE consortium, created in response to a call by the Innovative Medicines Initiative for the creation of a framework for a rapid benefit-risk assessment of vaccines, is expected to expand much of the groundwork delivered by PROTECT into the vaccine area. In the meanwhile there is a limited or no experience in the application of quantitative methods in the vaccine area. P95 had developed with SP-MSD a Multi-Criterion-Decision-Analysis (MCDA) model to evaluate the BR balance of the use of Gardasil, a vaccine to prevent HPV, in males. This talk will review the different steps that need to be taken when performing a quantitative BR assessment for a vaccine using the MCDA approach and how this compares to the more traditional (qualitative) frameworks such as PROACT-URL. The challenges encountered at each step will be highlighted, with focus on the construction of the value tree and the effects table, the assignment of values and weights and the scope of sensitivity analyses. For each of these, the approach that was followed and potential alternatives will be discussed. In the absence of clear guidance, choices were based on common sense and expert advice. Although sensitivity analyses can assess the impact of some of the choices made, future quantitative BR models for vaccines would profit from better guidance. This will benefit the transparency of the assessments and increase the vaccine community’s confidence in these models. Despite concern, at present the overall impact of such mutants seems to be low and they do not pose a public health threat or a need to modify the established hepatitis B vaccination programs. However, global surveillance networks are needed in order to better understand this issue.
Session 2
Case Studies of Benefit/Risk of Vaccines
(with historical examples)
The Rationale and Evidence Base Supporting the Vaccination of Frail/Elderly Rather than the «Transmitters» (Children/Young Adults) in Most Countries

Lone SIMONSEN
George Washington University

Almost 10 years have passed since a first batch of research and publications questioned the body of evidence that claimed extremely large benefits of influenza vaccine in the elderly, so that vaccine programs would save 1 elderly person’s death for every ~200 vaccine doses given to elderly persons each season. Subsequently a fierce battle ensued in the literature, focused on whether or not the observational studies published in major journals and over decades all suffered from severe confounding bias that had led to massive overestimation of vaccine benefits. With this realization, researchers began incorporating strategies for bias reduction into their study design to get a more accurate measure of the effectiveness of influenza vaccine in the elderly. Randomized controlled trials were not an option due to ethical concerns as influenza vaccine was thought to be highly effective in seniors; and even so, important outcomes like influenza-related death would require a very large number of study participants.

In this presentation I will review the decade long controversy, the frameworks now used for bias-detection and bias-adjustment, and finally the current best measurements of vaccine effectiveness in the elderly and the effect on vaccine policy and vaccine product development.

Incidentally, because influenza is strongly winter-seasonal the insights about creating bias-free measurements of influenza vaccine effectiveness due to the opportunity to define “ground truth” temporal periods pre-influenza where no effect of the intervention should exist. The story should therefore be of broad interest as the unique temporal influenza exposure pattern offers important lessons for statistical model adjustment in observational studies that are widely used to document effect of interventions in any disease area where the disease is not strongly temporal and where randomized controlled studies are not available.
Human Papilloma Virus Vaccination, a Benefit Risk Balance Evaluation

Pieter NEELS, MD
Vaccine Advice BVBA / NDA Advisory Board

The benefit risk analysis is today the driving force at regulatory agencies to approve new medicinal products, or to re-evaluate an old product. This exercise is not always easy as for some products the benefit or the causality of the risk is not easy to define.

In almost all cases, cervical cancer is caused by a Human papilloma virus infection and the human immune system is not very efficacious in protecting against these wild virus intracellular infections. Two pharmaceutical companies have developed a vaccine in order to try to prevent infection with the wild virus. And with success!

However is preventing wild virus infection, persistent infection of 6 months or 12 months, preventing cancer?

Cervical cancer as an outcome is not a good parameter to measure in clinical trials, not from an ethical nor from a practical viewpoint. Both vaccines have been developed and registered based on a surrogate marker for protection, namely CIN 2+ (Cervical intraepithelial neoplasia) lesions. Most of these lesions when found and not treated will develop to a cervical cancer and thus the prevention of these lesions was thought to be a good surrogate for efficacy.

However due to the high efficacy of these vaccines, no (or extremely rare) CIN lesions are seen in the vaccinated group. How will new generation vaccines be evaluated on benefit risk, as too few cases will occur in the groups.
Rotavirus: Benefits/Risks Assessment in Different Parts of the World

Umesh D. PARASHAR
CDC, Atlanta GA

Clinical trials of the two currently licensed rotavirus vaccines – RotaTeq and Rotarix -- enrolled more than 60,000 infants each to examine whether these live oral vaccines were associated with intussusception, the rare complication that in 1999 forced the withdrawal of the first licensed rotavirus vaccine, Rotashield. The trials found no increased intussusception risk with either vaccine however, further post-marketing surveillance was recommended. Rotavirus vaccines are recommended for immunization of children worldwide and their introduction into the national immunization programs of over 50 countries has shown tremendous health benefits. At the same time, surveillance in many countries – the United States, Australia, Mexico, and Brazil – has also detected a small but significant increase in intussusception risk, primarily in the 1-7 days immediately following the first immunization. The overall risk appears to be in the order of about 1 to 5 excess intussusception cases in 100,000 vaccinated infants. Policy makers in various countries and global bodies, including the World Health Organization, have reviewed these data and concluded that the risk is low compared with the large health benefits of vaccination and have, therefore, not made any changes to rotavirus vaccine recommendations. It is unclear if the findings of intussusception risk from high- and middle-income countries extend to low-income countries. Furthermore, despite lower efficacy, the public health benefits of rotavirus vaccines in low-income settings, where the vast majority of deaths from rotavirus occur, are likely to be substantial and outweigh a small intussusception risk.
Polio (Benefit/Risk as a Function of Time; OPV vs IPV)

Joel CALMET
Sanofi Pasteur

Polio Eradication is a unique Public Health exercise, with Smallpox as sole precedent in human health. Thus, it is possibly delicate to extrapolate with usual tools like benefit/risk analysis. However, a lot of lessons can be extracted, especially regarding policy making and the evolution of the contribution of the two possible vaccines of use (OPV and IPV) since the launch of the initiative in 1988.

The first key point was the choice of embarking into another eradication following the Smallpox triumph. Beyond scepticism, Polio has been preferred over Measles. Despite figures of disease burden largely in favour of Measles, it is likely that Polio choice has been based upon a mix of pragmatism and politics. Along the bumpy road of eradication, the choice of OPV came out initially as the sole exclusive tool and is now ending as an obstacle for the completion of eradication. The success of eradication and the absolute need for a zero case is however unique to this case.

In conclusion, the final case of polio will cost over $1 Billion and would hardly find support under a classical benefit/risk analysis. However, a recent evaluation counted the benefit of the initiative around $50 billion. This is not taking in account the legacy in terms of experience and capacity building just for surveillance. This is also ignoring that is a not so distant future all mothers in the world will never fear polio anymore for their children.
Vaccination of Pregnant Women: Benefits/Risks Assessment

Carol J. Baker, M.D.
Baylor College of Medicine, Houston, Texas, USA

Vaccination of pregnant women has been described for nearly 150 years. Examples from the USA include vaccine (1879), pertussis (1938), tetanus and influenza (1960s). These 3 vaccine protected pregnant women and their young infants from three life-threatening infections—smallpox, tetanus, and influenza with its complications of severe pneumonia and sepsis. From the outset, there was debate about what is now called benefit-risk ratio and vaccine uptake in pregnant women was meagre. Millions of maternal/newborn lives were saved by tetanus immunization during pregnancy and despite inadequate immediate supply by the pandemic influenza vaccine in 2009. Then the most significant adverse event in modern medicine, the thalidomide tragedy of the 1950’s, resulted in the attitude that anything a women was exposed to could harm the fetus. Any discussion of benefit from a vaccine for pregnant woman or her fetus/newborn was elipsed by the theoretical, often biologically implausible, possibility of risk.

After the thalidomide disaster, regulatory authorities in Europe and the US emphasized safety (risk) but excluded pregnant women from clinical trials guaranteeing that benefit from a medicine or vaccine was never assessed. Vaccines have not been developed for approval by regulatory bodies because of the inability to balance benefit and risk without data from manufacturers. However, two recent events have resulted in a paradigm shift: the influenza pandemic of 2009 and the neonatal and young infant deaths in the US, UK and Australia fro pertussis or whooping cough. Now these two vaccines are recommanded by advisory panels for use in pregnant women. This change has been driven by disease burden first and rationale with increasing safety data proving a shift from risk to benefit. As we move forward, certain questions should be addressed for this vulnerable population of women and infants.
Session 3
Future Development of Benefits/Risks Analysis
Data Needed for Benefits/Risks Assessment of Vaccines

Miriam STURKENBOOM
ERASMUS MC

In an era of rapid implementation of large scale immunization programs, near eradication of some pathogens and rapid changes in public confidence around vaccination programs it is critical to have the ability to support benefit-risk monitoring of vaccines real time to all decision makers. The ADVANCE project (Accelerated Development of Vaccine benefit-risk Collaboration in Europe) was initiated with the mission "to establish a prototype of a sustainable and compelling system that rapidly provides best available scientific evidence on vaccination benefits and risks post-licensure for well informed decisions. This will be achieved by developing and testing a code of conduct, rules of governance, technical infrastructures, data sources, methods, and workflows in a European network of stakeholders". ADVANCE is a unique collaboration between key players in the sector, including European Centre for Disease Prevention and Control (ECDC), European Medicines Agency (EMA), national public health and regulatory bodies, vaccine manufacturers, SMEs, and academic institutions.

In this presentation we will focus on initial work done in ADVANCE that was appraising the type of methods that have been developed in the small molecule area and their applicability to vaccines, some examples of benefit-risk assessments of vaccines and the data requirements to conduct population level benefit/risk assessments as well as individual level benefit/risk assessments.
Benefit-Risk assessment of vaccines, the perspective of a European regulatory agency

Christoph CONRAD
Paul-Ehrlich-Institut

The comparative evaluation or weighing of benefits (desired effects) and risks (undesired effects) is at the heart of decision-making in medicine and health care. In spite of common and frequent use of the concept of benefit risk assessment, so far, it has not been adequately defined nor is it easily quantifiable with a summary statistics. On top, some particularities of vaccines increase the complexity even further, e.g. usually, vaccines are given to healthy people with the aspiration of no risk at all and for some vaccines the benefit can be defined on the level of public health rather than for the vaccinated individual and not forgetting vaccines are complex biological medicinal products.

It is obvious, that considerations on benefit and risk are not only relevant for marketing authorization applications; they also apply to all development stages from the early clinical development to post authorization changes. Referring to the finding of an adventitious agent in a biological medicinal product, like the findings of porcine circovirus sequences or infectious circovirus in rotavirus vaccines in 2010 (Shasta D McClanahan, et al.; 2011) regulatory as well as public health decisions sometimes need to be done on the basis of incomplete or evolving data. WHO developed a guideline on Regulatory Risk Evaluation on Finding an Adventitious Agent in a Marketed Vaccine. From the perspective of a European regulatory agency the principles of this guideline will be discussed and framed in the context of a continuous benefit risk evaluation.
One of the primary responsibilities of the US Food and Drug Administration (FDA) is to ensure the availability of safe and effective human medical products, including vaccines. Marketing authorization by the US FDA requires that a vaccine be safe and effective for its intended use. Safety is relative, and thus not explicitly defined in the FDA statutes or regulations that govern marketing authorization in the US. However, recognizing that all medical interventions whether preventative or therapeutic carry some degree of risk of causing adverse effects, the safety of a vaccine is assessed by determining whether its benefits outweigh its potential risks. The FDA’s regulatory decisions in the pre-market and post-market review process are based on the assessment of benefits and risks of the product under review. The FDA considers not only the safety and effectiveness data submitted by the sponsor of a license application, but also considers other factors that may affect their assessment of benefit-risk. Other factors taken into consideration may include the nature and severity of the disease the vaccine is intended to treat or prevent, and the benefits and risks of other available interventions for the disease. This assessment is informed by the available scientific evidence and clinical judgment in accordance with applicable legal and regulatory standards. Although the FDA’s assessment encompasses both a quantitative and qualitative evaluation of scientific and clinical evidence, determining the acceptable degree of risk presents a challenge to regulators and medical policy makers.
An Industry Perspectives and Expectations on Benefits /Risks Assessment of Vaccines

Alena KHROMAVA
Sanofi Pasteur

Market authorization holders (MAH) are responsible for monitoring benefit-risk of their vaccines during clinical development and post-marketing. According to the new EU Pharmacovigilance Legislation and ICH E2C(R2), the MAH is responsible for vaccine benefit-risk evaluations in Periodic Benefit-Risk Evaluation Report (PBRER). Historically more emphasis was put on risk assessment (safety monitoring). Assessment of vaccine benefit comprises vaccine efficacy, vaccine effectiveness and impact on disease epidemiology. Evaluation of vaccine effectiveness typically relies on existing disease surveillance systems run by Ministries of Health, Public Health institutes, CDC / ECDC. Some systems have been developed primarily for safety monitoring (e.g., Vaccine Safety Datalink in the US). Typically, industry cannot directly access data funded and managed by the government(s) or public health. Developing public-private partnerships could be a solution. Through the European Innovative Medicines Initiative (IMI) project ADVANCE, the aim is to build an integrated and sustainable framework for continuous vaccine effect monitoring and evaluate the benefits and risks of vaccines. Within ADVANCE, public health, academic partners and European MAHs are building the framework together and defining its governance. Also getting the similar data on vaccines benefits and risks from low and middle-income countries (LMIC) where large linked databases may not be available still presents a challenge. Finally, efforts are underway to improve vaccine Pharmacovigilance systems in LMIC (WHO Blueprint, CIOMS Vaccine Safety working group).
Session 4
Beyond Benefits/Risks Assessment: Ethics/Choice/Decision-making
Vaccine Acceptance or Refusal: Individual Choice vs Societal Needs. 
Risk Communication: Risk vs. Benefit or Risk vs. Risk

Heidi J Larson, PhD
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Effective risk communication needs dialogue. Understanding perceptions of risk are as important as communicating scientific assessment of risk. This talk will examine the dynamics of dialogue as key to trust building and risk communication. Paul Slovic's triad of risk as science, as feeling, and as politics will be particularly examined.
Company B/R Decision-making process of Vaccines from early Development to Post Marketing Experience

Vincent BAUCHAU
GSK Vaccines

Benefit/risk (B/R) assessments play a critical role in many decisions by Vaccine Manufacturers. This presentation will summarise the reasons why Companies perform B/R assessments; which type of experts within the Companies contribute to the B/R assessments; what frameworks and methodologies are used; how decisions are typically made through multidisciplinary teams. This summary will be based on a recent survey of major Vaccine Manufacturers as part of the European IMI ADVANCE project. B/R assessments by Companies increasingly involve more systematic, if not quantitative B/R analyses. The various advantages of this approach as well as the multiple challenges will be illustrated. Challenges include interpretation and communication of the output of complex modelling exercises, managing several sources of uncertainty, dealing with the specificities of vaccines and a very dynamic environment, both from the regulatory and methodological sides.
Social Communication about Vaccines: from Conventional Media to Communication. “Vaccines”, “Anti-Vaccines” and “Anti-Anti-Vaccines” activism: the Role of Web 2.0 and the Traditional Mass Media

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Traditional mass media (newspaper, television and radio) and internet (particularly the Web 2.0) play an important role in the vaccines-society relationship. Among the main mechanisms that explain the social media impact, literature describes the “agenda-setting effect” (the selection of the problems or issues of concern, for a particular population at a given time) and the “framing effect” (the public representation and perception of problems and issues). Within the world of traditional media, journalists also act as “gatekeepers”, filtering their sources of information and the information itself. Gatekeeper function could be seen both as a positive and as a negative value (i.e.: “journalists help society looking for the truth” vs “there is an information bias produced by lobby’s influences”). As traditional media, Web 2.0 maintains agenda and framing effect but it has lost the gatekeeper role of journalism. Because of that, on social networks any person or organisation could potentially be a source of information. In the particular case of the information about vaccines, changes in the communication system produced during past decades have lead to the coexistence of three types of discourse at the public sphere: a) the discourse pursuing social awareness and acceptability of vaccination that appears intermittently in the occasion of public health campaigns; b) the discourse of rebellion represented by anti-vaccines activists (with a higher presence in social networks than in traditional media); and c) a more recent discourse promoted by the “anti-anti-vaccines” seeking primarily to refute the anti-vaccines arguments. Media surveillance systems are showing to be a useful tool to understand in deep this new landscape as well as for monitoring public concerns.
Ethical Analyses of Measures to Increase Vaccination Rates

Claudia EMERSON
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Routine immunization coverage remains low in many developing countries, leaving millions of children at risk of contracting vaccine-preventable infectious disease. Amongst the challenges to improving immunization coverage are i) the lack of parental motivation to vaccinate children, due in part to inadequate or misguided information about the risks and benefits of vaccines, and the ii) challenge of accurately determining which children have been vaccinated, what vaccines they have received, and how many doses were given and when. Current methods of assessing vaccine coverage are limited, notably because they fail to provide accurate and complete data about the vaccination status of individuals and sub-populations. Capturing children in transient and migrant populations is particularly challenging, and is critical in the last mile of polio eradication. Failing to ‘reach the unreached’ means further excluding and marginalizing a deeply vulnerable group. This presentation will examine, from an ethical perspective, some of the measures used to address these challenges, including compulsion, conditional cash transfers and other incentives used to motivate parents to vaccinate their children, and the use of innovative tracking and monitoring technologies aimed at capturing every last child.
Decision-making Framework of the German Standing Committee on Vaccination (STIKO)

Ole WICHMANN
Robert Koch Institute, Berlin

In most industrialized countries, national vaccine recommendations are developed by a National Immunization Technical Advisory Group (NITAG). A NITAG is an independent expert advisory committee, providing evidence-based recommendations to the Ministry of Health (MoH) or other national policy-makers to guide decisions on vaccine introduction and immunization strategies. In Germany, the Standing Committee on Vaccination (STIKO) was established in 1972 and currently consists of 17 members. The executive secretariat of STIKO is hosted by the Robert Koch Institute, which is an institution within the portfolio of the German MoH.

In 2012, STIKO has implemented a new decision-making framework, which was developed by the STIKO working group on methods. Core of this new framework for the development of evidence-based vaccination recommendation is the conduct of systematic reviews, meta-analyses, and grading the quality of evidence related to the vaccine characteristics: efficacy, effectiveness, and safety. The quality assessment is conducted by applying the “Grading of Recommendations Assessment, Development and Evaluation” (GRADE) methodology. Besides vaccine characteristics, key questions from four additional categories must be addressed when developing a recommendation: (i) pathogen characteristics; (ii) characteristics of the target disease (incl. disease burden and baseline risk); (iii) vaccination strategy (e.g. vaccination goal; vaccination coverage needed to achieve the goal; number-needed-to-vaccinate; expected population-level effects), and (iv) issues related to the implementation of the recommendation (e.g. demand/acceptance of the vaccine in the population; alternative preventive measures; cost-effectiveness if reliable analyses are available; systems in place to monitor the effects of vaccination).

The new framework was the first time successfully applied when STIKO developed a recommendation for routine rotavirus vaccination of infants in Germany, which was endorsed in 2013. To support a critical review and collaboration with other NITAGs, STIKO decided to publish comprehensive background papers both in English and German.
Key-Note 2: Social Sciences and the Vaccination Strategies in the Developing World

Anne-Marie MOULIN
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Vaccines were introduced at the Alma Ata Conference in 1978 as one of the universal measures, which would transform the sanitary worldwide status. Forty years later, the eradication plans based on vaccines are lagging behind the announced deadlines, but a globalizing world has witnessed the emergence of many new vaccines, targeting not only the epidemic diseases of the past but chronic diseases such as virus-induced cancers (e.g., hepatitis B and HPV-related cancer of the cervix).

Among the populations of the South, there is a raising concern about the vaccine strategies offered to them, which are often promoted from the outside, without clarification of the choices being made. There is also a growing suspicion of the procedures of clinical trials taking place in vulnerable populations. The issue of governance about the choice of public health strategies and the place of vaccines in these strategies and in the health systems is increasingly addressed and debated in the medias.

The benefit-risk analysis of the adoption of vaccines was debated since the earliest vaccines. With a growing knowledge of the complexity of the immune reactions we have a more precise grasp of the immune system’s doings, but also a clearer understanding of the complexity of biological phenomena, both at the individual and at the population level.

To avoid the disasters born from several misunderstandings happening in Africa and Asia, attention must be paid to the communication to an ever broader audience in the countries on the benefits and risks of vaccines of old or new vintage. I will discuss the examples of meningitis in Subsaharan countries, HPV vaccines in Africa, and polio in Central Asia.
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