COMMENTARY

Vaccination of children – summary and conclusions from a systematic review

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Sven-Arne Silfverdal1, Lennart Nilsson2, Margareta Blennow3, Rose-Marie Carlsson4, Lars Å Hanson5, Anders Lindberg6, Lars Lindquist7, Margaretha Magnusson3, Anders Norlund8, Olof Nyrén10, Per Olcén11, Patrick Olin12, Juliette Säwe13, Ann Söderström14, Birger Trollfors15, Åke Ortvist (ake.ortqvist@sll.se)16,17

1. Clinical Sciences, Pediatrics, Umeå University, Umeå, Sweden
2. Allergy Center and Pediatric Clinic, University Hospital, Linköping, Sweden
3. Sachs’ Childrens Hospital, Department of Clinical Science and Education, Stockholm South General Hospital, Stockholm, Sweden
4. Swedish Armed Forces, Centre for Defence Medicine, Gothenburg, Sweden
5. Emeritus, Department of Microbiology and Immunology, Gothenburg University, Göteborg, Sweden
6. Retired, County Medical Officer for Prevention and Control of Communicable Diseases, County Council of Halland, Halmstad, Sweden
7. Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden
8. Central Child Healthcare Unit, Uppsala Akademiska Hospital, Uppsala, Sweden
9. Department of Clinical Neuroscience, Division of Insurance Medicine, Karolinska Institutet, Stockholm, Sweden
10. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
11. Department of Laboratory Medicine/Microbiology, Örebro University Hospital, Örebro, Sweden
12. Retired from Swedish Institute for Infectious Diseases, Solna, Sweden
13. Swedish Council on Technology Assessment in Health Care, Stockholm, Sweden
14. Department of Communicable Disease Control, Västra Götaland, Kasernstorget, Göteborg, Sweden
15. Department of Paediatrics, Sahlgrenska University Hospital-East, Gothenburg, Sweden
16. Department of Communicable Diseases Control and Prevention, Stockholm, Sweden
17. Karolinska Institutet, Department of Medicine, Stockholm, Sweden

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Correspondence
Åke Ortqvist, M.D., Ph.D., Director, Department of Communicable Diseases Control and Prevention (Smittskyddsenheten), Box 17553, 118 91 Stockholm.
Tel: +46-8-7373921 | Fax: +46-8-315767 | Email: ake.ortqvist@sll.se

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Extensive vaccination programmes have eradicated smallpox globally and eliminated polio in nearly every country. Although the benefits of vaccination are indisputable, critical evaluation of childhood vaccinations is warranted, as these vaccines are recommended for all infants. In the late 1990s, a British physician raised suspicion about a possible correlation between measles vaccination and the development of autism. As a result of the uncertainty that arose among parents, the percentage of young children who received measles, mumps and rubella (MMR) vaccine declined in many countries; Sweden included. However, after several rigorous studies, the hypothesis of a causal relationship was refuted. This example illustrates the importance of providing complete and reliable information to parents, so they can be assured of making correct informed decisions about vaccinating their children.

In 2002, the Swedish Council on Technology Assessment in Health Care (SBU) was asked to review the published research covering some of the vaccines used in Sweden’s general vaccination programme. The primary objective was to examine the scientific evidence addressing the efficacy and safety of each of these vaccines, not to evaluate or design a new programme.

The review focused on vaccines against invasive disease due to Haemophilus influenzae type b (Hib), pertussis, measles, mumps, rubella, tuberculosis, hepatitis B, as well as combinations thereof. Diphtheria, tetanus and polio vaccines were part of the programme in 2008, but are not covered by the review (1).

The scientific literature was systematically reviewed by searching databases containing scientific publications, including primary study reports as well as systematic reviews covering articles published until June 2006. For each vaccine, the project group first agreed on criteria that a study must meet to be eligible for inclusion in the review, specifying the type of participants, vaccines and outcome...
measures. At least two reviewers examined all relevant publications independently using evaluation forms, designed specifically for each study type to appraise the validity of reported results. To ensure uniformity in the evaluation, detailed questions were asked about participant accrual, inclusion and exclusion criteria, main outcome, randomization procedure (for randomized controlled trials – RCTs), blinding, attrition, outcome assessment, selection and information bias as well as confounding, sample size calculation, power and statistical analysis. Using a score system, a priori determined weights (varying with seriousness of the threat to validity) were assigned to observed deviations from the ideally conducted study. The final synthesis of results from all relevant and valid studies, i.e. the overall scientific evidence for each conclusion, was graded from 1 to 3, where Evidence grade 1 indicates strong scientific evidence and grade 3 limited scientific evidence (for detailed information see Vaccination of children – a systematic review).

While the evaluation of vaccine efficacy was typically based on data from RCTs or large controlled observational studies of high-quality, the assessment of rare adverse events posed a greater challenge because efficacy studies are generally too small and the follow-up is too short. Even large-scale population-based observational studies may be too small to statistically verify an association, let alone to establish a causal relationship. Consequently, the project group could also include case reports on adverse events occurring after vaccination and applied criteria for causality (mainly temporality, biological gradient, plausibility, coherence, experimental evidence and analogy) proposed by Bradford Hill and recommended by Institute of Medicine and WHO Global Advisory Committee on Vaccine Safety. Formal evidence grading of such information was not possible.

EVIDENCED-BASED RESULTS FROM THE SYSTEMATIC REVIEW

- **Vaccination for Hib effectively protects against invasive Hib infections** (Evidence grade 1). Vaccine efficacy lasts for at least 3 years. Vaccination against Hib reduces the carrier rate of Hib in the pharynx in children and reduces the frequency of serious Hib infections even in unvaccinated people (herd immunity) (Evidence grade 3). Studies have not documented any causal relationship between Hib conjugate vaccines and serious adverse events, e.g. death, sudden infant death syndrome, seizures, type 1 diabetes mellitus or Guillain–Barré syndrome.

- **Vaccination for pertussis protects children against pertussis** (Evidence grade 1). Vaccine efficacy lasts for at least 5 years after administration of three or four doses of acellular pertussis vaccine (Evidence grade 3). Routine vaccination programmes that include acellular pertussis vaccine reduce the need of hospitalization for pertussis among vaccinated children younger than 2 years of age (Evidence grade 3). The scientific literature does not provide support for causal relationships between pertussis vaccine and a handful of serious adverse events described in case reports or national reports of adverse events. There is no evidence of higher frequency of serious bacterial infections, or deaths from such infections, after vaccination with acellular pertussis vaccine, but the statistical power of available studies to detect small elevations in cause-specific mortality was limited.

- **The combined measles, mumps, and rubella (MMR) vaccine currently administered protects against all three diseases and their complications** (Evidence grade 3).

- **Mumps and rubella vaccine increases the risk of febrile seizures during the first 2 weeks after vaccination, when fever is frequent, but does not increase the risk of later seizures** (Evidence grade 3). MMR vaccine does not cause type 1 diabetes or serious infections that require hospitalization (Evidence grade 3). MMR vaccine does not cause autism or autism spectrum disorder (Evidence grade 3).

- **Vaccination for hepatitis B protects children against hepatitis B** (Evidence grade 1). More than 90% of children who are vaccinated develop protective antibody levels after the first dose (Evidence grade 1). Serious hypersensitivity reactions have been reported following hepatitis B vaccination, but are rare. The scientific evidence is insufficient to rule out or confirm an association between hepatitis B vaccination and multiple sclerosis (MS), although most data speak against such an association.

- **Vaccine against tuberculosis (with Bacille Calmette Guérin, BCG) administered during the neonatal period or shortly thereafter protects children against tuberculosis** until they are at least 5 years of age. Protection against all types of tuberculosis is approximately 75% (Evidence grade 2). Efficacy against disseminated (miliary) tuberculosis and tuberculous meningitis is 75–85% (Evidence grade 2). Fatal disseminated BCG infection has been reported after BCG vaccination, but rarely. This condition develops most often in children who have a rare genetic immunodeficiency disease, which increases the risk for other diseases as well.

- **Studies of combination vaccines present no indication of clinically significant differences in the frequency of redness or swelling after administration of combinations containing the following vaccines: diphtheria, tetanus, pertussis, polio, hepatitis B and Hib** (Evidence grade 2). Overall, the literature provides no compelling support for causal relationships between vaccination with combination vaccines and the very occasional serious adverse events, including death, described in case reports or national reports of adverse events.

**COMMENT**

The project’s objective was to review the efficacy and adverse effects of individual vaccines, or combinations of
vaccines, used within a vaccination programme. This included scrutiny of clinical trials of vaccines and follow-up studies of vaccinated children. All vaccines studied in this review were found to be highly efficacious in preventing disease, although in some instances the evidence grades were low. The efficacy of individual vaccines can only be assessed by means of randomized controlled trials that compare vaccinated and unvaccinated children.

The effectiveness of a vaccine when used within a general vaccination programme is, however, generally analysed by observing the target disease incidence before and after introduction of the intervention. Such studies are by definition observational and thus sensitive to confounding by factors that vary across calendar periods. Therefore, conclusions based exclusively on results from such studies cannot be assigned the highest evidence grade unless the change is so striking that effects of confounding, if any, could not materially change the overall conclusion. Nevertheless, the coherence of observational data from many countries persuasively demonstrates that vaccination has reduced and even eradicated disease.

Assessments of adverse effects, particularly those that are rare and serious, face similar methodological difficulties:

- Controlled studies can never be large enough to rule out very small risks.
- Suspicion of an association between MMR vaccination and autism was persuasively refuted by a nationwide Danish study that used record linkages between a national vaccination register and multiple demographic and health care registers. However, notwithstanding the meticulousness of this study, it was observational and thus liable to residual confounding. Therefore, a conclusion based on this study alone cannot attain the highest evidence grade.
- Observational studies that use individuals as their own controls, comparing adverse event frequency in time windows during which the effect of the vaccination is exerted to the frequency in time windows when this effect is inconceivable (before or long after vaccination), are prone to selection bias, survival bias and detection bias, along with possible confounding by factors that vary with calendar period. Hence, even though such studies may elegantly demonstrate excesses in event incidence after vaccinations, e.g. fever and seizures within 48 h after pertussis vaccination, or seizures within 7–14 days after measles vaccination, conclusions based exclusively on their results cannot attain the highest evidence grade.

Therefore, it is important to ensure more reliable data and higher quality in reporting on effectiveness and adverse events. In Sweden, a necessary basis for surveillance and evaluation of vaccination programmes is the establishment of a national vaccination register and improved reporting of adverse events that can be linked to this register. Another important issue involves improved methods for case ascertainment to further ensure the quality in reporting.

For further information about SBU’s systematic reviews and grading of evidence, see http://www.sbu.se/en/Assessment-and-Evidence/.

Reference
