

# Measles Vaccines Position Paper, Aug 2009

## Key references in alphabetic order with summaries, when available

**Acharya A, Diaz-Ortega JL, Tambini G, de Quadros C, Arita I. Cost-effectiveness of measles elimination in Latin America and the Caribbean: a prospective analysis. Vaccine. 2002 Sep 10;20(27-28):3332-41.**

**BACKGROUND:** In 1994, the Americas set a goal of interrupting indigenous measles transmission from the Western Hemisphere by 2000. To accomplish this goal, the Pan American Health Organization (PAHO) developed an enhanced measles vaccination strategy. **METHODS:** Cost data was collected at PAHO for Latin American and Caribbean (LAC) countries covering 96% of the region's population on components of the routine programs, and the 'follow-up' activities from member countries. In order to interpret our findings we have compared the present scenario regarding measles with one that would have ensued if past trends continued. **RESULTS:** For the entire LAC population, estimated cost of elimination program will be US\$ 571 million in present value terms.

**INTERPRETATION:** The vaccination strategy toward achieving elimination of measles costs USD 244 million, incremental from the cost of vaccination before the elimination program. Within 2000-2020, the current program will have prevented the occurrence of 3.2 million cases of measles and 16,000 deaths. Thus, vaccination strategy prevents a single case of measles at the cost of USD 71.75 and prevents a death due to measles at the cost of USD 15,000. The case fatality rate depends on a well functioning treatment program for measles cases. The vaccination strategy saves a total of USD 208 million in treatments costs due to reduced incidence of measles.

**Beeler J, Varricchio F, Wise R. Thrombocytopenia after immunization with measles vaccines: review of the vaccine adverse events reporting system (1990 to 1994). Pediatr Infect Dis J 1996;15:88-90.**

**Black SB, Cimino CO, Hansen J, Lewis E, Ray P, Corsaro B, Graepel J, Laufer D. Immunogenicity and safety of measles-mumps-rubella, varicella and Haemophilus influenzae type b vaccines administered concurrently with a fourth dose of heptavalent pneumococcal conjugate vaccine compared with the vaccines administered without heptavalent pneumococcal conjugate vaccine. Pediatr Infect Dis J. 2006 Apr;25(4):306-11.**

**BACKGROUND:** Prevnar [heptavalent pneumococcal conjugate vaccine (PCV7)] is licensed in the United States for routine administration in infants and may be coadministered with other infant vaccines. Safety and immunogenicity data on the coadministration of the fourth dose of PCV7 with measles-mumps-rubella (MMR), varicella and Haemophilus influenzae type b (Hib) vaccines are limited. **METHODS:** Children 12-15 months of age received either MMR with PCV7 (group 1) or MMR without PCV7 (group 2). All subjects received Hib and varicella vaccines. Group 2 received PCV7 6-9 weeks after MMR vaccination. Sera for analysis of all non-PCV7 antibodies were collected just before administration of MMR vaccine and 6 weeks later. Optimal antigen responses were assessed with the use of predetermined antibody titers.

The primary end point was >90% response rate (all antigens). Noninferiority was defined as <10% difference between groups. Local and systemic reactions and postvaccination adverse events were monitored and compared between groups. RESULTS: A total of 694 subjects (347 per group) were enrolled. After immunization with MMR plus PCV7 concurrently, or MMR followed 6 weeks later by PCV7, the percentages of subjects seroconverting were significantly greater than 90% for all antigens. The difference between the 2 groups was significantly less than 10%. CONCLUSION: The immune response to MMR, Hib and varicella vaccines, when administered concurrently with a 4<sup>th</sup> (booster) dose of PCV7, was noninferior to that of these vaccines when given without PCV7. These results support concomitant administration of PCV7 with MMR, varicella and Hib as part of the recommended immunization schedule for children 12-15 months of age.

**Brenzel L, Wolfson LJ, Fox-Rushby J et al. Disease control priorities in developing countries (chapter 20). In: Cairns KL, Perry R, Ryman T, et al, eds. *Vaccine-preventable diseases*. The International Bank for Reconstruction and Development / The World Bank, 2006: 389–411 (<http://files.dcp2.org/pdf/expressbooks/vaccine.pdf>; accessed July 2009).**

**Caceres VM, Strebel PM, Sutter RW. Factors determining prevalence of maternal antibody to MV throughout infancy: a review. *Clin Infect Dis* 2000;31:110-9.**

The effectiveness of vaccination against measles, the leading cause of vaccine-preventable deaths in infants globally, is greatly impacted by the level of maternal antibody to measles virus (or "measles maternal antibody"; MMA) during infancy. Variation in the prevalence of maternal antibody to measles virus between infant populations across countries and sociodemographic strata is poorly understood. We reviewed the literature on the prevalence of MMA, focusing on 3 principal determinants: starting level of maternal antibody, placental transfer of maternal antibody, and rate of decay of maternal antibody after birth. Our review identified placental transfer as an important determinant, with greater efficiency found in studies performed in developed countries. Placental transfer was influenced by gestational age, human immunodeficiency virus infection, and malaria. Antibody levels in mothers varied widely between countries, although predictably according to vaccination status within populations. Rates of antibody decay across studies were similar. Future studies should evaluate the utility of the cord blood level of MMA as a predictor of vaccine efficacy in infancy; inclusion of World Health Organization international reference sera will facilitate comparisons. Greater understanding of the determinants of the prevalence of MMA will help national policy makers determine the appropriate age for measles vaccination.

**Campbell H, Andrews N, Brown KE, Miller E. Review of the effect of measles vaccination on the epidemiology of SSPE. *International Journal of Epidemiology*, 2007, 36:1334–1348.**

BACKGROUND: When measles vaccines were widely introduced in the 1970s, there were concerns that they might cause subacute sclerosing panencephalitis (SSPE): a very rare, late-onset, neurological complication of natural measles infection. Therefore, SSPE registries and routine measles immunization were established in many countries

concurrently. We conducted a comprehensive review of the impact of measles immunization on the epidemiology of SSPE and examined epidemiological evidence on whether there was any vaccine-associated risk. METHODS: Published epidemiological data on SSPE, national SSPE incidence, measles incidence and vaccine coverage, reports of SSPE in pregnancy or shortly post partum were reviewed. Potential adverse relationships between measles vaccines and SSPE were examined using available data. RESULTS: Epidemiological data showed that successful measles immunization programmes protect against SSPE and, consistent with virological data, that measles vaccine virus does not cause SSPE. Measles vaccine does not: accelerate the course of SSPE; trigger SSPE or cause SSPE in those with an established benign persistent wild measles infection. Evidence points to wild virus causing SSPE in cases which have been immunized and have had no known natural measles infection. Perinatal measles infection may result in SSPE with a short onset latency and fulminant course. Such cases are very rare. SSPE during pregnancy appears to be fulminant. Infants born to mothers with SSPE have not been subsequently diagnosed with SSPE themselves. CONCLUSIONS: Successful measles vaccination programmes directly and indirectly protect the population against SSPE and have the potential to eliminate SSPE through the elimination of measles. Epidemiological and virological data suggest that measles vaccine does not cause SSPE.

**CDC, April 2008. What Clinicians Need to Know About MMRV Vaccine Safety.**  
<http://www.cdc.gov/vaccinesafety/vsd/mmr.htm>

**Commission on Macroeconomics and Health. Macroeconomics and health: investing in health for economic development. Boston: Center for International Development at Harvard University, 2001. Access 13 May 2009 at:**  
<http://whqlibdoc.who.int/publications/2001/924154550x.pdf>

**Dayan GH, Cairns L, Sangrujee N, Mtonga A, Nguyen V, Strebel P. Cost-effectiveness of three different vaccination strategies against measles in Zambian children. Vaccine. 2004 Jan 2;22(3-4):475-84.**

The vaccination program in Zambia includes one dose of measles vaccine at 9 months of age. The objective of this study was to compare the cost-effectiveness of the current one-dose measles vaccination program with an immunization schedule in which a second dose is provided either through routine health services or through supplemental immunization activities (SIAs). We simulated the expected cost and impact of the vaccination strategies for an annual cohort of 400,000 children, assuming 80% vaccination coverage in both routine and SIAs and an analytic horizon of 15 years. A vaccination program which includes SIAs reaching children not previously vaccinated would prevent an additional 29,242 measles cases and 1462 deaths for each vaccinated birth cohort when compared with a one-dose program. Given the parameters established for this analysis, such a program would be cost-saving and the most cost-effective vaccination strategy for Zambia.

**Demicheli V, Jefferson T, Rivetti A, Price D. Vaccines for measles, mumps and rubella in children. Cochrane Database Syst Rev. 2005 Oct 19;(4):**

**BACKGROUND:** Public debate over the safety of the trivalent measles, mumps and rubella (MMR) vaccine, and the resultant drop in vaccination rates in several countries, persists despite its almost universal use and accepted effectiveness. **OBJECTIVES:** We carried out a systematic review to assess the evidence of effectiveness and unintended effects associated with MMR. **SEARCH STRATEGY:** We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 4, 2004), MEDLINE (1966 to December 2004), EMBASE (1974 to December 2004), Biological Abstracts (from 1985 to December 2004), and Science Citation Index (from 1980 to December 2004). Results from reviews, handsearching and from the consultation of manufacturers and authors were also used. **SELECTION CRITERIA:** Eligible studies were comparative prospective or retrospective trials testing the effects of MMR compared to placebo, do-nothing or a combination of measles, mumps and rubella antigens on healthy individuals up to 15 years of age. These studies were carried out or published by 2004. **DATA COLLECTION AND ANALYSIS:** We identified 139 articles possibly satisfying our inclusion criteria and included 31 in the review. **MAIN RESULTS:** MMR was associated with a lower incidence of upper respiratory tract infections, a higher incidence of irritability, and similar incidence of other adverse effects compared to placebo. The vaccine was likely to be associated with benign thrombocytopenic purpura, parotitis, joint and limb complaints, febrile convulsions within two weeks of vaccination and aseptic meningitis (mumps) (Urabe strain-containing MMR). Exposure to MMR was unlikely to be associated with Crohn's disease, ulcerative colitis, autism or aseptic meningitis (mumps) (Jeryl-Lynn strain-containing MMR). We could not identify studies assessing the effectiveness of MMR that fulfilled our inclusion criteria even though the impact of mass immunisation on the elimination of the diseases has been largely demonstrated. **AUTHORS' CONCLUSIONS:** The design and reporting of safety outcomes in MMR vaccine studies, both pre- and post-marketing, are largely inadequate. The evidence of adverse events following immunisation with MMR cannot be separated from its role in preventing the target diseases.

**de Swart RL, Yuksel S, Osterhaus AD. Relative contributions of measles virus hemagglutinin- and fusion protein-specific serum antibodies to virus neutralization. *Journal of Virology*, 2005, 79:11547–115451.**

The relative contribution of measles virus hemagglutinin (H)- or fusion protein (F)-specific antibodies to virus neutralization (VN) has not been demonstrated. We have depleted these specific antibodies from sera collected from young adults, who had been vaccinated during childhood, by prolonged incubation with viable transfected human melanoma cells expressing H or F. Simultaneous depletion of antibodies of both specificities completely abrogated VN activity. Depletion of F-specific antibodies only had a minimal effect, whereas removal of H-specific antibodies resulted in almost complete reduction of VN activity. These results demonstrate that measles virus neutralizing antibodies are mainly directed to the H protein.

**Duclos P, Ward BJ. Measles vaccines: a review of adverse events. *Drug Saf.* 1998 Dec;19(6):435-54.**

A great deal of controversy has recently been generated over the publication of several articles implicating measles vaccine in the induction of Crohn's disease and autism. The publication of this work has already had a negative impact on measles vaccine acceptance in the UK. These allegations are particularly troubling because they arise in the context of increased use of measles vaccine as global control of measles nears and the international community considers strategies for a drive towards eradication. In 1994, the US Institute of Medicine reviewed the world literature and published a comprehensive review of adverse events associated with measles-containing vaccines. Reviewing the literature published between 1994 and the present day, reveals that there is considerable new data suggesting that modified gelatin rather than egg proteins is responsible for most episodes of anaphylaxis following measles vaccination. New work weakens the possible links between measles vaccine and subacute sclerosing panencephalitis and Guillain-Barré syndrome, but strengthens the rare association of measles-containing vaccines with post infectious encephalomyelitis. The alleged associations between measles vaccination and Crohn's disease and autism are based upon weak science and have largely been refuted by a large volume of stronger work. A review of the data generated in the last 4 years amply demonstrates the continued efforts of the scientific community to monitor and understand true measles vaccine-associated adverse events. The rapidity and clarity of this same community's debunking of the spurious associations with Crohn's disease and autism suggests that those charged with vaccination programmes have learned from past mistakes. During 30 years of worldwide use, measles vaccination has proven to be one of the safest and most successful health interventions in the history of mankind. It is not a 'perfect' vaccine, but the benefits of measles vaccination far outweigh the risks even in countries with low incidence of measles and high rates of measles vaccine coverage.

**Edejer TT, Aikins M, Black R, Wolfson L, Hutubessy R, Evans DB. Cost effectiveness analysis of strategies for child health in developing countries. BMJ. 2005 Nov 19;331(7526):1177.**

**OBJECTIVE:** To determine the costs and effectiveness of selected child health interventions-namely, case management of pneumonia, oral rehydration therapy, supplementation or fortification of staple foods with vitamin A or zinc, provision of supplementary food with counselling on nutrition, and immunisation against measles. **DESIGN:** Cost effectiveness analysis. **DATA SOURCES:** Efficacy data came from published systematic reviews and before and after evaluations of programmes. For resource inputs, quantities came from literature and expert opinion, and prices from the World Health Organization Choosing Interventions that are Cost Effective (WHO-CHOICE) database, **RESULTS:** Cost effectiveness ratios clustered in three groups, with fortification with zinc or vitamin A as the most cost effective intervention, and provision of supplementary food and counselling on nutrition as the least cost effective. Between these were oral rehydration therapy, case management of pneumonia, vitamin A or zinc supplementation, and measles immunisation. **CONCLUSIONS:** On the grounds of cost effectiveness, micronutrients and measles immunisation should be provided routinely to all children, in addition to oral rehydration therapy and case management of pneumonia for those who are sick. The challenge of malnutrition is not well addressed by existing interventions.

**Elliman D, Sengupta N, El Bashir H, and Bedford H. Child health. Measles, mumps, and rubella prevention. ClinicalEvidence. Web publication date: 01 Feb 2007. [http://clinicalevidence.bmj.com/ceweb/conditions/chd/0316/0316\\_I1.jsp](http://clinicalevidence.bmj.com/ceweb/conditions/chd/0316/0316_I1.jsp)**

**Fiedler JL, Chuko T. The cost of Child Health Days: a case study of Ethiopia's Enhanced Outreach Strategy (EOS). Health Policy Plan. 2008 Jul;23(4):222-33.**

Child Health Days (CHDs) are twice-annual campaign-style events designed to increase the coverage of vitamin A and one or more other child health services. Although more than two dozen countries have had a CHD, little has been published about them. This paper presents an activity-based costing study of Ethiopia's version of CHDs, the Enhanced Outreach Strategy (EOS). The December 2006 round reached more than 10 million beneficiaries at an average cost per beneficiary of US\$0.56. When measles is added, the cost of the package doubles. Given the way the distribution day delivery system and the service package are structured, there are economies of scope. Because most of the costs are determined by the number of delivery sites and are independent of the number of beneficiaries, other things equal, increasing the beneficiaries would reduce the average cost per beneficiary. Taking into account only the mortality impact of vitamin A, EOS saved 20,200 lives and averted 230,000 DALYs of children 6-59 months. The average cost per life saved was US\$228 and the cost per DALY averted was equivalent to 6% of per capita GDP (US\$9), making the EOS cost-effective, according to WHO criteria. While CHDs are generally construed as a temporary strategy for improving coverage of supply-constrained systems, inadequate attention has been paid to demand-side considerations that suggest CHDs have an important role to play in changing care-seeking behaviour, in increasing community organization and participation, and in promoting district autonomy and capacity. Recognition of these effects suggests the need for decisions about where and when to introduce, and when to end, a CHD to take into account more than 'just' health sector considerations: they are more broadly about community development. UNICEF played a key role in initiating the EOS and finances 68% of costs, raising concern about the programme's long-term sustainability.

**Gatchalian S, Yao Y, Zhou B, Zhang L, Yoksan S, Kelly K, Neuzil KM, Yaïch M, Jacobson J. Comparison of the immunogenicity and safety of measles vaccine administered alone or with live, attenuated Japanese encephalitis SA 14-14-2 vaccine in Philippine infants. Vaccine. 2008 Apr 24;26(18):2234-41.**

Japanese encephalitis (JE) virus is a major cause of disease, disability, and death in Asia. An effective, live, attenuated JE vaccine (LJEV) is available; however, its use in routine immunization schedules is hampered by lack of data on concomitant administration with measles vaccine (MV). This study evaluated the immunogenicity and reactogenicity of LJEV and MV when administered at the same or separate study visits in infants younger than 1 year of age. Three groups of healthy infants were randomized to receive LJEV at age of 8 months and MV at 9 months (Group 1; n=100); MV and LJEV together at 9 months (Group 2; n=236); or MV and LJEV at 9 and 10 months, respectively (Group 3; n=235). Blood was obtained 4 weeks after each vaccine administration to determine antibody levels for measles and JE. Reactogenicity was assessed by parental diaries and clinic visits. Four weeks after immunization, measles seroprotection rates (defined as  $\geq$  or  $\geq$  340 mIU/ml) were high and comparable in all three groups and specifically, rates in the

combined MV-LJEV (Group 2) were not statistically inferior to those in Group 3 receiving MV separately (96% versus 100%, respectively). Likewise, the LJEV seroprotection rates were high and similar between the three groups. The reactogenicity profiles of the three vaccine schedules were also analogous. LJEV and MV administered together are well tolerated and immunogenic in infants younger than 1 year. These results should facilitate incorporation of LJEV into routine immunization schedules with MV.

**Grais RF, DE Radiguès X, Dubray C, Fermon F, Guerin PJ. Exploring the time to intervene with a reactive mass vaccination campaign in measles epidemics. *Epidemiol Infect.* 2006 Aug;134(4):845-9.**

The current WHO policy during measles outbreaks focuses on case management rather than reactive vaccination campaigns in urban areas of resource-poor countries having low vaccine coverage. Vaccination campaigns may be costly, or not timely enough to impact significantly on morbidity and mortality. We explored the time available for intervention during two recent epidemics. Our analysis suggests that the spread of measles in African urban settings may not be as fast as expected. Examining measles epidemic spread in Kinshasa (DRC), and Niamey (Niger) reveals a progression of smaller epidemics. Intervening with a mass campaign or in areas where cases have not yet been reported could slow the epidemic spread. The results of this preliminary analysis illustrate the importance of revisiting outbreak response plans.

**Huiming Y, Chaomin W, Meng M. Vitamin A for treating measles in children. *Cochrane Database Syst Rev.* 2005 Oct 19;(4):CD001479.**

**BACKGROUND:** Measles is a major cause of childhood morbidity and mortality. Vitamin A deficiency is a recognized risk factor for severe measles infections. The World Health Organization (WHO) recommends administration of an oral dose of vitamin A (200,000 international units (IU), or 100,000 IU in infants) each day for two days to children with measles when they live in areas where vitamin A deficiency may be present.

**OBJECTIVES:** To determine whether vitamin A therapy, commenced after measles has been diagnosed, is beneficial in preventing mortality, pneumonia and other secondary complications in children. **SEARCH STRATEGY:** We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 1, 2005), MEDLINE (1966 to March 2005), EMBASE (1980 to December 2004) and looked for unpublished studies. **SELECTION CRITERIA:** Only randomized controlled trials in which children with measles were given vitamin A or placebo along with standard treatment were considered. **DATA COLLECTION AND ANALYSIS:** Studies were assessed independently by two authors. The analysis of dichotomous outcomes was done using the StatXact software and results expressed as relative risk (RR) with 95% confidence interval (CI). Subgroup analyses were carried out for dose, formulation, age, hospitalization and pneumonia-specific mortality. Weighted mean differences (WMD) with 95% CI were calculated for continuous outcomes. **MAIN RESULTS:** There was no significant reduction in the risk of mortality in the vitamin A group when all the studies were pooled using the random-effects model (RR 0.70; 95% CI 0.42 to 1.15). Using two doses of vitamin A (200,000 IU) on consecutive days was associated with a reduction in the risk of mortality in children under the age of two years (RR 0.18; 95% CI 0.03 to 0.61) and a reduction in the risk of pneumonia-specific mortality (RR 0.33; 95% CI 0.08 to 0.92). There was no evidence that vitamin A in a single dose was associated with a reduced risk of mortality

among children with measles. There was a reduction in the incidence of croup (RR 0.53; 95% CI 0.29 to 0.89) but no significant reduction in the incidence of pneumonia (RR 0.92; 95% CI 0.69 to 1.22) or diarrhoea (RR 0.80; 95% CI 0.27 to 2.34) with two doses.

**AUTHORS' CONCLUSIONS:** Although we found no overall significant reduction in mortality with vitamin A therapy for children with measles there was evidence that two doses were associated with a reduced risk of mortality and pneumonia-specific mortality in children under the age of two years. There were no trials that directly compared a single dose with two doses.

**Pannuti CS, Morello RJ, Moraes JC, Curti SP, Afonso AM, Camargo MC, Souza VA. Identification of primary and secondary measles vaccine failures by measurement of immunoglobulin G avidity in measles cases during the 1997 São Paulo epidemic. Clin Diagn Lab Immunol. 2004 Jan;11(1):119-22**

Despite almost universal use of measles vaccines in recent decades, epidemics of the disease continue to occur. Understanding the role of primary vaccine failure (failure to seroconvert after vaccination) and secondary vaccine failures (waning immunity after seroconversion) in measles epidemics is important for the evaluation of measles control programs in developing countries. After a measles epidemic in São Paulo, Brazil, 159 cases previously confirmed by detection of specific immunoglobulin M (IgM) antibodies were tested for IgG avidity, and a secondary immune response, defined by an IgG avidity index of at least 30%, was established in 30 of 159 (18.9%) patients. Among the 159 patients, 107 (67.3%) had not been vaccinated and 52 (32.7%) had received one or more doses of measles vaccine. Of the 107 unvaccinated patients, 104 (97.2%) showed a primary immune response, defined as an IgG avidity index of less than 30%. Among the 52 patients with documented vaccination, 25 (48.1%) showed a primary immune response and 27 (51.9%) showed a secondary immune response, thereby constituting a secondary vaccine failure. Primary vaccine failure was observed in 13 of 13 patients vaccinated prior to 1 year of age and in 43.5 and 12.5%, respectively, of patients receiving one or two doses after their first birthdays. These results provide evidence that measurement of IgG avidity can be used to distinguish between primary and secondary vaccine failures in vaccinated patients with measles; the method can also be a useful tool for the evaluation of measles control programs.

**Parks CL, Lerch RA, Walpita P, Wang HP, Sidhu MS, Udem SA. Comparison of predicted amino acid sequences of MV strains in the Edmonston vaccine lineage. J Virol 2001;75:910-20.**

Protein-encoding nucleotide sequences of the N, P, M, F, H, and L genes were determined for a low-passage isolate of the Edmonston wild-type (wt) measles virus and five Edmonston-derived vaccine virus strains, including AIK-C, Moraten, Schwarz, Rubeovax, and Zagreb. Comparative analysis demonstrated a high degree of nucleotide sequence homology; vaccine viruses differed at most by 0.3% from the Edmonston wt strain. Deduced amino acid sequences predicted substitutions in all viral polypeptides. Eight amino acid coding changes were common to all vaccine viruses; an additional two were conserved in all vaccine strains except Zagreb. Comparisons made between vaccine strains indicated that commercial vaccine lots of Moraten and Schwarz had identical coding regions and were closely related to Rubeovax, while AIK-C and Zagreb diverged from the Edmonston wt along slightly different paths. These comparisons also revealed amino acid

coding substitutions in Moraten and Schwarz that were absent from the closely related reagentogenic Rubeovax strain. All of the vaccine viruses contained amino acid coding changes in the core components of the virus-encoded transcription and replication apparatus. This observation, combined with identification of noncoding region nucleotide changes in potential cis-acting sequences of the vaccine strains (C. L. Parks, R. A. Lerch, P. Walpita, H.-P. Wang, M. S. Sidhu, and S. A. Udem, *J. Virol.* 75:921-933, 2001), suggest that modulation of transcription and replication plays an important role in attenuation.

**Paunio M, Hedman K, Davidkin I, Peltola H. IgG avidity to distinguish secondary from primary measles vaccination failures: prospects for a more effective global measles elimination strategy. *Expert Opin Pharmacother.* 2003 Aug;4(8):1215-25**

The nearly 40-year long debate on the relevance of secondary measles vaccination failure has been inconclusive because a feasible method for the assessment of the duration of immunity has been lacking. Even if a two-dose measles vaccination policy is now universally endorsed, WHO still officially adheres to the view that a single successful measles vaccination, without natural boosters, induces a lifelong immunity and deems secondary failures epidemiologically irrelevant - in the belief that the latter are rare and do not participate in the transmission chain. A recently published study on measles-IgG avidity, which allows for separation of secondary from primary vaccination failures, tentatively showed that the official view does not necessarily hold true. The results may have wide implications on global measles eradication efforts. The potential of IgG avidity measurement in complex postvaccination measles epidemiology is discussed.

**Pelletier L, Chung P, Duclos P, Manga P, Scott J. A benefit-cost analysis of two-dose measles immunization in Canada. *Vaccine.* 1998 May-Jun;16(9-10):989-96.**

In 1992, because of the limitations of the one-dose measles immunization program, the National Advisory Committee on Immunization (NACI) recommended a two-dose measles immunization program to eliminate measles. More recently, NACI recommended also a special catch-up program to prevent predicted measles outbreaks and to achieve an earlier elimination of measles. The objective of this study was to complete a benefit-cost analysis of a two-dose immunization program with and without a mass catch-up campaign compared with the current one-dose program. The resulting benefit: cost ratios vary between 2.61:1 and 4.31:1 depending on the strategy used and the age of the children targeted. Given the parameters established for this analysis, the benefits of a second-dose vaccination program against measles far outweigh the costs of such a program under all scenarios.

**Rota PA, Featherstone DA, Bellini WJ. Molecular epidemiology of measles virus. *Current Topics in Microbiology and Immunology*, 2009, 330:129–150.**

Genetic characterization of wild-type measles viruses provides a means to study the transmission pathways of the virus and is an essential component of laboratory-based surveillance. Laboratory-based surveillance for measles and rubella, including genetic characterization of wild-type viruses, is performed throughout the world by the WHO Measles and Rubella Laboratory Network, which serves 166 countries in all WHO regions. In particular, the genetic data can help confirm the sources of virus or suggest a source for

unknown-source cases as well as to establish links, or lack thereof, between various cases and outbreaks. Virologic surveillance has helped to document the interruption of transmission of endemic measles in some regions. Thus, molecular characterization of measles viruses has provided a valuable tool for measuring the effectiveness of measles control programs, and virologic surveillance needs to be expanded in all areas of the world and conducted during all phases of measles control.

**Salisbury DM, Campbell H, Edwards B. Measles rubella immunisation campaign in England – one year on. London: Department of Health, November 1995.**

**Stowe J, Andrews N, Taylor B, Miller E. No evidence of an increase of bacterial and viral infections following Measles, Mumps and Rubella vaccine. *Vaccine*. 2009 Feb 25;27(9):1422-5.**

The suggestion that multi-antigen vaccines might overload the immune system has led to calls for single antigen vaccines. In 2003 we showed that rather than an increase there appeared to be a reduced risk of severe bacterial infection in the three months following Measles, Mumps and Rubella vaccine (MMR). The present analysis of illnesses in a general population is based on an additional 10 years of data for bacterial infections and also includes admissions with viral infections. Analyses were carried out using the self-controlled case-series method and separately for bacterial and viral infection cases, using risk periods of 0-30 days, 31-60 days and 61-90 days post MMR vaccine. An analysis was also carried out for those cases which were given MMR and Meningococcal serogroup C (MCC) vaccines concomitantly. A reduced risk was seen in the 0-30-day period for both bacterial infection (relative incidence=0.68, 95% CI 0.54-0.86) and viral infections (relative incidence=0.68, 95% CI 0.49-0.93). There was no increased risk in any period when looking at combined viral or bacterial infections or for individual infections with the single exception of an increased risk in the 31-60 days post vaccination period for herpes infections (relative incidence=1.69, 95% CI 1.06-2.70). For the children given Meningococcal group C vaccines concomitantly no significantly increased risk was seen in either the bacterial (relative incidence=0.54, 95% CI 0.26-1.13) or viral cases (relative incidence=0.46, 95% CI 0.11-1.93). Our study confirms that the MMR vaccine does not increase the risk of invasive bacterial or viral infection in the 90 days after the vaccination and does not support the hypothesis that there is an induced immune deficiency due to overload from multi-antigen vaccines.

**Strebel P M, Papania MJ, Dayan G H, Halsey N A. Measles vaccine, Chapter 18, pp 352-398: In S. Plotkin, W. Orenstein, P. Offit (Eds): *Vaccines*, 5 Ed. Saunders Elsevier, 2008.**

**Van Damme W, Van Lerberghe W. Strengthening health services to control epidemics: empirical evidence from Guinea on its cost-effectiveness. *Trop Med Int Health*. 2004 Feb;9(2):281-91.**

**OBJECTIVE:** To assess the cost-effectiveness of control measures implemented against epidemics in Guinea, West Africa. **METHODS:** We collected all routine data available on incidence, mortality, control measures implemented and their cost during epidemics of cholera, measles and meningococcal meningitis in 1993-95. Then we estimated for one prefecture the effectiveness and cost-effectiveness of epidemic control measures for three scenarios: (i) 'natural' situation, (ii) 'routine' health services and (iii) 'intervention'. Where uncertainty was considerable, we used sensitivity analysis and estimated ranges. **FINDINGS:** Routine health services reduced potential deaths by 51% (67%, 37% and 60% for cholera, measles and meningitis, respectively), and additional interventions further decreased potential deaths by 28% (28%, 27% and 30% for cholera, measles and meningitis, respectively). The marginal cost-effectiveness of epidemic control measures in routine health services was US dollars 29 per death averted. The marginal cost-effectiveness of additional interventions was US dollars 93 per death averted. **CONCLUSION:** Even with the data weaknesses that characterize situations of epidemics it is possible to show that strengthening health services to control epidemics as was performed in Guinea was highly cost-effective. Moreover, sensitivity analysis over a range of assumptions confirms that (i) well-functioning health services averted the major part of avoidable deaths, (ii) combining existing health services with additional interventions minimizes the health impact of epidemics and (iii) case management should be a cornerstone of control of epidemics of cholera, measles and meningococcal meningitis.

**Vijayaraghavan M, Lievano F, Cairns L, Wolfson L, Nandy R, Ansari A, Golaz A, Mashal T, Salama P. Economic evaluation of measles catch-up and follow-up campaigns in Afghanistan in 2002 and 2003. *Disasters*. 2006 Jun;30(2):256-69.**

This paper assesses the cost-effectiveness of, and the return on the investment in, the 2002 catch-up and the 2003 follow-up measles campaigns in Afghanistan from the perspective of the donor. The catch-up campaign targeted nearly 12 million children aged between six months and 12 years, while the follow-up campaign targeted over five million children aged between 9 and 59 months. Both campaigns successfully vaccinated approximately 96 per cent of the respective target populations, and are expected to avert an estimated 301,000 measles deaths over the next 10 years. The average cost per dose of measles vaccine delivered was USD 0.40. The cost per death prevented is USD 23.6, assuming a case fatality rate of 10 per cent and a discount rate of three per cent. With more than 42,000 measles deaths avoided for every one million US dollars spent, the campaigns are an excellent public health investment for precluding childhood mortality in a country affected by a complex emergency.

**WHO: Safety and immunogenicity of measles vaccine in HIV-infected children: a systematic review and meta-analysis. Report presented to the Global Advisory Committee on Vaccine Safety (GACVS), June 2009. *Wkly Epidemiol Rec*. 2009; 84, 325-332.**

**World Health Organization, 2009. The Immunological basis for immunization series. Module 7: Measles, update 2009.**  
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**Wolfson LJ, Grais RF, Luquero FJ, Birmingham ME, Strebel PM. Estimates of measles case fatality ratios: a comprehensive review of community-based studies. Int J Epidemiol. 2009 Feb;38(1):192-205.**

**BACKGROUND:** Global deaths from measles have decreased notably in past decades, due to both increases in immunization rates and decreases in measles case fatality ratios (CFRs). While some aspects of the reduction in measles mortality can be monitored through increases in immunization coverage, estimating the level of measles deaths (in absolute terms) is problematic, particularly since incidence-based methods of estimation rely on accurate measures of measles CFRs. These ratios vary widely by geographic and epidemiologic context and even within the same community from year-to-year.

**METHODS:** To understand better the variations in CFRs, we reviewed community-based studies published between 1980 and 2008 reporting age-specific measles CFRs.

**RESULTS:** The results of the search consistently document that measles CFRs are highest in unvaccinated children under age 5 years; in outbreaks; the lowest CFRs occur in vaccinated children regardless of setting. The broad range of case and death definitions, study populations and geography highlight the complexities in extrapolating results for global public health planning. **CONCLUSIONS:** Values for measles CFRs remain imprecise, resulting in continued uncertainty about the actual toll measles exacts.

**Zepp F, Behre U, Kindler K, Laakmann KH, Pankow-Culot H, Mannhardt-Laakmann W, Beckers F, Descamps D, Willems P. Immunogenicity and safety of a tetravalent measles-mumps-rubella-varicella vaccine co-administered with a booster dose of a combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-Haemophilus influenzae type b conjugate vaccine in healthy children aged 12-23 months. Eur J Pediatr. 2007 Aug;166(8):857-64.**

This study was undertaken to assess the co-administration of an experimental measles-mumps-rubella-varicella vaccine (MMRV, GlaxoSmithKline Biologicals) with a combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-Haemophilus influenzae type b conjugate (DTPa-HBV-IPV/Hib) vaccine in healthy children. Healthy children aged 12-23 months (N = 451) were randomised to one of three parallel groups to receive one dose of MMRV vaccine co-administered with a booster dose of DTPa-HBV-IPV/Hib vaccine (co-administration group), or one dose of MMRV vaccine alone (MMRV group), or a booster dose of DTPa-HBV-IPV/Hib vaccine alone (DTPa-HBV-IPV/Hib group). No differences in seroconversion rates for measles (>95%), mumps (>80%), rubella (>99%) and varicella (>98%) were seen between the co-administration group and the MMRV group. No differences in geometric mean titres (GMTs) were observed between the two groups with the exception of anti-measles titres, which were observed to be higher in the MMRV group than in the co-administration group (4,419.2 vs. 3,441.8 mIU/ml respectively). Immune response to the booster dose of DTPa-HBV-IPV/Hib vaccine was observed to be similar in the co-administration group and the DTPa-HBV-IPV/Hib group. Co-administration of the MMRV vaccine with a booster dose of DTPa-HBV-IPV/Hib vaccine was well-tolerated and did not exacerbate the reactogenicity profile of either vaccine. In summary, GlaxoSmithKline Biologicals' experimental MMRV vaccine was immunogenic and well-tolerated when administered with a booster dose of DTPa-HBV-IPV/Hib vaccine during the second year of life. The ability to co-administer the MMRV vaccine at the same time as other routine childhood immunisation vaccines could increase compliance with varicella vaccination in countries where this vaccine is already recommended and may facilitate implementation of varicella vaccination elsewhere.

**Zhou F, Reef S, Massoudi M, Papania MJ, Yusuf HR, Bardenheier B, Zimmerman L, McCauley MM. An economic analysis of the current universal 2-dose measles-mumps-rubella vaccination program in the United States. J Infect Dis. 2004 May 1;189 Suppl 1:S131-45.**

To evaluate the economic impact of the current 2-dose measles-mumps-rubella (MMR) vaccination program in the United States, a decision tree-based analysis was conducted with population-based vaccination coverage and disease incidence data. All costs were estimated for a hypothetical US birth cohort of 3803295 infants born in 2001. The 2-dose MMR vaccination program was cost-saving from both the direct cost and societal perspectives compared with the absence of MMR vaccination, with net savings (net present value) from the direct cost and societal perspectives of US dollars 3.5 billion and US dollars 7.6 billion, respectively. The direct and societal benefit-cost ratios for the MMR vaccination program were 14.2 and 26.0. Analysis of the incremental benefit-cost of the second dose showed that direct and societal benefit-cost ratios were 0.31 and 0.49, respectively. Varying the proportion of vaccines purchased and administered in the public

versus the private sector had little effect on the results. From both perspectives under even the most conservative assumptions, the national 2-dose MMR vaccination program is highly cost-beneficial and results in substantial cost savings.