References Measles vaccines: WHO position paper – March 2017
(References with abstracts cited in the position paper in the order of appearance.)

Guidance for the development of evidence-based vaccine-related recommendations. http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf; accessed January 2017.

(No abstract available.)

WEEKLY EPIDEMIOLOGICAL RECORD, NO. 35, 28 AUGUST 2009, 84, pp. 349–360. Measles vaccines: WHO position paper.

(No abstract available.)

Strebel PM et al. Measles vaccine. In: Plotkin S, Orenstein W, Offit P, eds. Vaccines, 2016.

(No abstract available.)

WEEKLY EPIDEMIOLOGICAL RECORD, NO. 45, 11 NOVEMBER 2016, 91, 525-536. Progress towards regional measles elimination – worldwide, 2000–2015.

(No abstract available.)

Rota PA et al., Measles. Nat Rev Dis Primers. 2016 Jul 14;2:16049.

Measles is an infectious disease in humans caused by the measles virus (MeV). Before the introduction of an effective measles vaccine, virtually everyone experienced measles during childhood. Symptoms of measles include fever and maculopapular skin rash accompanied by cough, coryza and/or conjunctivitis. MeV causes immunosuppression, and severe sequelae of measles include pneumonia, gastroenteritis, blindness, measles inclusion body encephalitis and subacute sclerosing panencephalitis. Case confirmation depends on clinical presentation and results of laboratory tests, including the detection of anti-MeV IgM antibodies and/or viral RNA. All current measles vaccines contain a live attenuated strain of MeV, and great progress has been made to increase global vaccination coverage to drive down the incidence of measles. However, endemic transmission continues in many parts of the world. Measles remains a considerable cause of childhood mortality worldwide, with estimates that >100,000 fatal cases occur each year. Case fatality ratio estimates vary from <0.01% in industrialized countries to >5% in developing countries. All six WHO regions have set goals to eliminate endemic transmission of MeV by achieving and maintaining high levels of vaccination coverage accompanied by a sensitive surveillance system. Because of the availability of a highly effective and relatively inexpensive vaccine, the monotypic nature of the virus and the lack of an animal reservoir, measles is considered a candidate for eradication.

Global eradication of measles: report by the Secretariat. World Health Organization, Geneva, Switzerland, 2010. http://apps.who.int/gb/ebwha/pdf_files/wha63/a63_18-en.pdf, accessed January 2017.

(No abstract available.)

WHO. Global Vaccine Action Plan 2011-2020.

http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/; accessed December 2016.

(No abstract available.)

Pan American Health Organization. Plan of Action for Maintaining Measles, Rubella, and Congenital Rubella Syndrome Elimination in the Region of the Americas: Final Report [Internet]. 55th Direction Council; 66th session of the WHO Regional Committee for the Americas; 26-30 September 2016; Washington, DC. Washington, DC: PAHO; 2012 (Resolution CD55/INF/10). http://www.paho.org/hq/index.php?option=com_content&view=article&id=12528%3Aregion-americas-declared-free-measles; accessed Dec 2016.

(No abstract available.)

Thompson, K. M. Evolution and use of dynamic transmission models for measles and rubella risk and policy analysis. Risk Analysis 2016; 36(7):1383-1403.

The devastation caused by periodic measles outbreaks motivated efforts over more than a century to mathematically model measles disease and transmission. Following the identification of rubella, which similarly presents with fever and rash and causes congenital rubella syndrome (CRS) in infants born to women first infected with rubella early in pregnancy, modelers also began to characterize rubella disease and transmission. Despite the relatively large literature, no comprehensive review to date provides an overview of dynamic transmission models for measles and rubella developed to support risk and policy analysis. This systematic review of the literature identifies quantitative measles and/or rubella dynamic transmission models and characterizes key insights relevant for prospective modeling efforts. Overall, measles and rubella represent some of the relatively simplest viruses to model due to their ability to impact only humans and the apparent life-long immunity that follows survival of infection and/or protection by vaccination, although complexities arise due to maternal antibodies and heterogeneity in mixing and some models considered potential waning immunity and reinfection. This review finds significant underreporting of measles and rubella infections and widespread recognition of the importance of achieving and maintaining high population immunity to stop and prevent measles and rubella transmission. The significantly lower transmissibility of rubella compared to measles implies that all countries could eliminate rubella and CRS by using combination of measles- and rubella-containing vaccines (MRCVs) as they strive to meet regional measles elimination goals, which leads to the recommendation of changing the formulation of national measles-containing vaccines from measles only to MRCV as the standard of care.

De Serres, Gay NJ, Farrington CP. Epidemiology of transmissible diseases after elimination. Am J Epidemiol 2000; 151: 1039-1048.

Elimination of an infectious disease is often understood to mean the total absence of cases in a population. This situation can occur only if the entire population is immune as a result of either natural disease or vaccination. However, this costly and unrealistic scenario is not necessary to ensure elimination, more appropriately defined as a situation in which sustained transmission cannot occur and secondary spread from importations of disease will end naturally, without intervention. The authors describe the size and duration of outbreaks caused by imported infections after indigenous transmission has been eliminated. They show that the status of the elimination process can be monitored by assessing the proportion of cases imported and the distribution of outbreak sizes. Measles in Canada, the United States, and the United Kingdom provides a good example of the relevance of these criteria. Surveillance of the size and duration of these outbreaks

enables maintenance of elimination to be monitored.

Module 7: measles update 2009. Geneva, World Health Organization. The Immunological basis for immunization series. http://www.who.int/immunization/documents/ISBN9789241597555/en/index.html; accessed January 2017.

(No abstract available.)

de Swart RL et al., 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.

WEEKLY EPIDEMIOLOGICAL RECORD, NO. 18, 6 MAY 2016, 91, pp. 240-246. Global measles and rubella laboratory network support for elimination goals, 2010–2015.

(No abstract available.)

Fitzgerald TL et al., Measles with a possible 23 day incubation period. Communicable Diseases Intelligence. 2012; 36: 277-280.

Measles virus (MV) eradication is biologically, technically and operationally feasible. An essential feature in understanding the chain of MV transmission is its incubation period, that is, the time from infection to the onset of symptoms. This period is important for determining the likely source of infection and directing public health measures to interrupt ongoing transmission. Long measles incubation periods have rarely been documented in the literature. We report on a previously healthy 11-year-old Australian boy who was confirmed with measles genotype D9 infection following travel in the Philippines. Epidemiological evidence supported an unusually long incubation period of at least 23 days and virological evidence was consistent with this finding. Although public health control measures such as post exposure prophylaxis, isolation and surveillance of susceptible individuals should continue to be based on the more common incubation period, a longer incubation period may occasionally explain an unexpected measles case.

Griffin, D. E. in Fields Virology (eds Fields, B. N., Howley, P. M., Cohen, J. I. & Knipe, D. M.) pp. 1042–1069 (Wolters Kluver/Lippincott Williams & Wilkins, 2013) Robbins FC. Measles: clinical features. Pathogenesis, pathology and complications. Am J Dis Child. 1962 Mar;103:266–73.

(No abstract available.)

Perry RT and Halsey NA. The Clinical Significance of Measles: A Review. J Infect Dis. 2004 May 1;189(Supplement 1):S4–16.

Forty years after effective vaccines were licensed, measles continues to cause death and severe disease in children worldwide. Complications from measles can occur in almost every organ system. Pneumonia, croup, and encephalitis are common causes of death; encephalitis is the most common cause of long-term sequelae. Measles remains a common cause of blindness in developing countries. Complication rates are higher in those <5 and >20 years old, although croup and otitis media are more common in those <2 years old and encephalitis in older children and adults. Complication rates are increased by immune deficiency disorders, malnutrition, vitamin A deficiency, intense exposures to measles, and lack of previous measles vaccination. Case-fatality rates have decreased with improvements in socioeconomic status in many countries but remain high in developing countries.

Campbell H et al., 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.

Wolfson, LJ et al.; Estimates of measles case fatality ratios: a comprehensive review of community-based studies. Int. J. Epidemiol. 2009;38, 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.

Palumbo P et al., Population-based study of measles and measles immunization in human immunodeficiency virus-infected children. Pediatr Infect Dis J. 1992 Dec;11(12):1008–14.

This study reports the course of measles and results of measles immunization in a cohort of human immunodeficiencyvirus-infected children. Six cases of measles were identified. All had typical clinical manifestations, 5 of 6 developed pneumonia and 3 of 6 died. A measles intervention program consisting of serologic screening and active immunization (measles-mumps-rubella (MMR)) was instituted in 1990. Among 127 children with data available for analysis (mean age, 6.7 years), only 35% had documentation of prior immunization with MMR. Among 80 children who had preimmunization measles serology reported, 56% were measles antibody-negative and 40% were antibody-positive; following intervention 36% remained measles antibody-negative.
Six children lost measles antibody over time. MMR nonresponders had lower CD4 lymphocyte counts (303 +/- 394) compared with responders (865 +/- 677; P = 0.0058). Measles is a potentially fatal illness in human immunodeficiency virus-infected children. Prevention strategies are limited by low rates of age-appropriate MMR immunization, poor antibody responses to MMR in older human immunodeficiency virus-infectedchildren and seroreversion.

Treating Measles in Children. Geneva: World Health Organization, 1996; http://apps.who.int/iris/handle/10665/63706; accessed December 2016.

(No abstract available.)

Garly M-L et al., Prophylactic antibiotics to prevent pneumonia and other complications after measles: community based randomised double blind placebo controlled trial in Guinea-Bissau. BMJ. 2006 December 16;333(7581):1245.

OBJECTIVE:
To investigate whether prophylactic antibiotics can prevent complications of measles.
DESIGN:
Community based, randomised, double blind, placebo controlled trial.
SETTING:
Bandim Health Project study area in Bissau, Guinea-Bissau, west Africa.
PARTICIPANTS:
84 patients with measles during a measles epidemic in Bissau in 1998 (fewer than originally planned owing to interruption by war).
INTERVENTIONS:
Sulfamethoxazole-trimethoprim (co-trimoxazole) or placebo for seven days.
MAIN OUTCOME MEASURES:
Pneumonia and admission to hospital. Also weight change during the first month of infection, diarrhoea, severe fever, oral thrush, stomatitis, conjunctivitis, and otitis media.

RESULTS:
The median age of the patients with measles was 5.4 (range 0.49-24.8) years. One of 46 participants who received co-trimoxazole developed pneumonia, in contrast to six of 38 participants who received placebo (odds ratio 0.08 (95% confidence interval 0 to 0.56), adjusted for age group). The number needed to treat was 7 (4 to 48). All three participants admitted to hospital had received placebo (P=0.09). The weight gain during the first month after inclusion was 15 (2-29) g/day in the placebo group and 32 (23-42) g/day in the co-trimoxazole group (P=0.04, adjusted for age group, weight for age at inclusion, measles vaccination status, and duration of disease). Significantly less conjunctivitis occurred among recipients of co-trimoxazole than placebo, as well as a non-significant tendency to less diarrhoea, severe fever, oral thrush, and stomatitis. Complications of otitis media were the same in the two groups.
CONCLUSIONS:
The group that received prophylactic antibiotics had less pneumonia and conjunctivitis and had significantly higher weight gains in the month after inclusion. The results indicate
that prophylactic antibiotics may have an important role in the management of measles infection in low income countries.

Vitamin A supplementation in infants and children 6–59 months of age. http://www.who.int/elena/titles/guidance_summaries/vitamina_children/en/, accessed February 2017.

(No abstract available.)

McLean HQ et al., Centers for Disease Control and Prevention. Prevention of Measles, Rubella, Congenital Rubella Syndrome, and Mumps, 2013: Summary Recommendations of the Advisor Committee on Immunization Practices (ACIP). MMWR. 2013 Jun 14;62(RR-04): 1-34.

This report is a compendium of all current recommendations for the prevention of measles, rubella, congenital rubella syndrome (CRS), and mumps. The report presents the recent revisions adopted by the Advisory Committee on Immunization Practices (ACIP) on October 24, 2012, and also summarizes all existing ACIP recommendations that have been published previously during 1998-2011 (CDC. Measles, mumps, and rubella--vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 1998;47[No. RR-8]; CDC. Revised ACIP recommendation for avoiding pregnancy after receiving a rubellacontaining vaccine. MMWR 2001;50:1117; CDC. Updated recommendations of the Advisory Committee on Immunization Practices [ACIP] for the control and elimination of mumps. MMWR 2006;55:629-30; and, CDC. Immunization of healthcare personnel: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2011;60[No. RR-7]). Currently, ACIP recommends 2 doses of MMR vaccine routinely for children with the first dose administered at age 12 through 15 months and the second dose administered at age 4 through 6 years before school entry. Two doses are recommended for adults at high risk for exposure and transmission (e.g., students attending colleges or other post-high school educational institutions, healthcare personnel, and international travelers) and 1 dose for other adults aged ≥18 years. For prevention of rubella, 1 dose of MMR vaccine is recommended for persons aged ≥12 months. At the October 24, 2012 meeting, ACIP adopted the following revisions, which are published here for the first time. These included: • For acceptable evidence of immunity, removing documentation of physician diagnosed disease as an acceptable criterion for evidence of immunity for measles and mumps, and including laboratory confirmation of disease as a criterion for acceptable evidence of immunity for measles, rubella, and mumps. For persons with human immunodeficiency virus (HIV) infection, expanding recommendations for vaccination to all persons aged ≥12 months with HIV infection who do not have evidence of current

severe immunosuppression; recommending revaccination of persons with perinatal HIV infection who were vaccinated before establishment of effective antiretroviral therapy (ART) with 2 appropriately spaced doses of MMR vaccine once effective ART has been established; and changing the recommended timing of the 2 doses of MMR vaccine for HIV-infected persons to age 12 through 15 months and 4 through 6 years. For measles postexposure prophylaxis, expanding recommendations for use of immune globulin administered intramuscularly (IGIM) to include infants aged birth to 6 months exposed to measles; increasing the recommended dose of IGIM for immunocompetent persons; and recommending use of immune globulin administered intravenously (IGIV) for severely immunocompromised persons and pregnant women without evidence of measles immunity who are exposed to measles. As a compendium of all current recommendations for the prevention of measles, rubella, congenital rubella syndrome (CRS), and mumps, the information in this report is intended for use by clinicians as baseline guidance for scheduling of vaccinations for these conditions and considerations regarding vaccination of special populations. ACIP recommendations are reviewed periodically and are revised as indicated when new information becomes available.

Knudsen KM et al., Child mortality following standard, medium or high titre measles immunization in West Africa. Int J Epidemiol. 1996 Jun;25(3):665-73.

BACKGROUND:
The World Health Organization (WHO) recommended the use of high titre measles vaccine in 1989. Subsequent long term follow-up of several trials yielded results suggesting higher mortality among children inoculated with medium and high titre vaccines compared to standard titre vaccines, although none of the individual trials found significant differences in mortality.
METHODS:
Long term survival after standard, medium and high titre measles vaccines has been investigated in a combined analysis of all West African trials with mortality data. In trials from Guinea-Bissau, The Gambia and Senegal, children received medium or high titre vaccines from 4 months of age and were compared to control groups recruited at the same time later receiving standard titre vaccine from 9 months of age. All children were followed up to at least 3 years old.
RESULTS:
Combining trials of high titre vaccines showed higher mortality among the high titre group compared to the standard group: mortality ratio (MR) = 1.33 (95% CI : 1.02-1. 73). Mortality among recipients of medium titre vaccines was not different from that in the standard vaccine group, MR = 1.11 (95% CI: 0.54-2.27). In a combined analysis by sex, the adjusted mortality ratios comparing high titre vaccine with standard vaccine were 1.86 (95% CI : 1.28-2.70) for females and 0.91 (95% CI : 0.61-1.35) for males. The trials were not designed to study long term mortality. Adjustments for several possible sources of bias did not alter the results.
CONCLUSIONS:
The combined analysis showed a decreased survival related to high titre measles vaccine compared with standard titre vaccines, though solely among females. As a result of these studies from West Africa and a study from Haiti, WHO has recommended that high titre measles vaccine no longer be used.
PIP:
A prospective survey of the use of high and medium-titre measles vaccine in Guinea-Bissau, the Gambia, and Senegal indicated that this regimen is associated with higher long-term child mortality than the standard titre vaccine. Children enrolled in trials in these three countries received medium or high-titre vaccines at three months of age and survival data were compared to findings from controls who received the standard titre at nine months of age. There were 339 deaths among the 3073 children (11,129 child-years) followed for up to three years of age. Combination of all West African data for medium and high-titre vaccines yielded a mortality rate of 1.21 (95% confidence

interval, 0.89-1.63). The excess mortality was statistically significant at the p 0.05 level only when high-titre vaccine was compared to the standard regimen (1.33; 95% confidence interval, 1.02-1.73). No difference in mortality was found between medium or high-titre recipients and control children who had not yet received any vaccine. The excess mortality in the high-titre groups was restricted to females. There was no interaction between age and vaccine type. As a result of these findings, the World Health Organization reversed its 1989 recommendation for use of high-titre measles vaccine. Urged are community studies of measles-related morbidity and mortality that investigate the gender differential identified in this survey.

Parks CL et al.,Comparison of predicted amino acid sequences of MV strains in the Edmonston vaccine lineage. Journal of Virology. 2001;75:910–920.

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 polypetides. 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 reactogenic 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.

WHO. Requirements for measles, mumps and rubella vaccines and combined vaccine (live). WHO Technical Report Series, No. 840, 1994, Annex 3. http://www.who.int/biologicals/publications/trs/areas/vaccines/mmr/WHO_TRS_840_A3.pdf?ua=1; accessed December 2016.

(No abstract available.)

Mina et al., Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality. Science. 2015 May 8;348(6235):694-9.

Immunosuppression after measles is known to predispose people to opportunistic infections for a period of several weeks to months. Using population-level data, we show that measles has a more prolonged effect on host resistance, extending over 2 to 3 years. We find that nonmeasles infectious disease mortality in high-income countries is tightly coupled to measles incidence at this lag, in both the pre- and post-vaccine eras. We conclude that long-term immunologic sequelae of measles drive interannual fluctuations in nonmeasles deaths. This is consistent with recent experimental work that attributes the immunosuppressive effects of measles to depletion of B and T lymphocytes. Our data provide an explanation for the long-term benefits of measles vaccination in preventing all-cause infectious disease. By preventing measles-associated immune memory loss, vaccination protects polymicrobial herd immunity.

Stowe J et al., No evidence of an increase of bacterial and viral infections following Measles, Mumps and Rubella vaccine. Vaccine.2009;27:1422–1425.

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 followingMeasles, 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.

WEEKLY EPIDEMIOLOGICAL RECORD, NO. 21, 23 MAY 2014, 89, pp 221-236. Meeting of the Strategic Advisory Group of Experts on immunization, April 2014 – conclusions and recommendations.

(No abstract available.)

Caceres VM et al., Factors determining prevalence of maternal antibody to MV throughout infancy: a review. Clinical Infectious Diseases. 2000, 31:110–119.

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.

Uzicanin A and Zimmerman L, Field effectiveness of live attenuated measles-containing vaccines: a review of published literature. J Infect Dis. 2011 Jul;204 Suppl 1:S133–48.

BACKGROUND
Information on measles vaccine effectiveness (VE) is critical to help inform policies for future global measles control goals.
METHODS:
We reviewed results of VE studies published during 1960-2010.
RESULTS:
Seventy papers with 135 VE point estimates were identified. For a single dose of vaccine administered at 9-11 months of age and ≥12 months, the median VE was 77.0% (interquartile range [IQR], 62%-91%) and 92.0% (IQR, 86%-96%), respectively. When analysis was restricted to include only point estimates for which vaccination history was verified and cases were laboratory confirmed, the median VE was 84.0% (IQR, 72.0%-95.0%) and 92.5% (IQR, 84.8%-97.0%) when vaccine was received at 9-11 and ≥12 months, respectively. Published VE vary by World Health Organization region, with generally lower estimates in countries belonging to the African and SouthEast Asian Regions. For 2 doses of measles-containing vaccine, compared with no vaccination, the median VE was 94.1% (IQR, 88.3%-98.3%).
CONCLUSIONS:
The VE of the first dose of measles-containing vaccine administered at 9-11 months was lower than what would be expected from serologic evaluations but was higher than expected when administered at ≥12 months. The median VE increased in a subset of articles in which classification bias was reduced through verified vaccination history and laboratory confirmation. In general, 2 doses of measles-containing vaccine provided excellent protection against measles.

GRADE table I: Effectiveness of measles vaccine in young children and adolescents. http://www.who.int/immunization/documents/measles_grad_effectiveness.pdf?ua=1, accessed January 2017.

(No abstract available.)

GRADE table II: Safety and immunogenicity in HIV infected children. http://www.who.int/immunization/measles_grad_HIV.pdf?ua=1, , accessed January 2017.

(No abstract available.)

Report to SAGE on Evidence Supporting Measles Revaccination for HIV infected Children Receiving Highly Active Antiretroviral Therapy. http://www.who.int/immunization/sage/meetings/2015/october/7_Measles_Revaccination_HIV_Infected_Children_Report_SAGE_26_September_2015.pdf?ua=1, accessed January 2017.

(No abstract available.)

Davidkin I et al., Persistence of measles, mumps, and rubella antibodies in an MMR-vaccinated cohort: a 20-year follow-up. J Infect Dis. 2008;197: 950–56.

BACKGROUND:
The persistence of antibodies against measles, mumps, and rubella induced by the measles-mumps-rubella (MMR) vaccine and the kinetics of antibody decline after the second MMR vaccine dose were studied in the same cohort for 20 years.
METHODS:
Measles, mumps, and rubella antibodies were measured by enzyme immunoassay in 20-year follow-up serum samples (n= 183) of twice-vaccinated individuals, and measles antibodies were also

measured in oral fluids (n = 177). Antibody decay was determined in a group (n = 58) with subsequent samples collected 1, 8, and 15 years after the second MMR dose.
RESULTS:
In total, 95%, 74%, and 100% of 183 vaccinees were still seropositive for measles, mumps, and rubella, respectively, and 85% of 177 vaccinees had measurable measles antibodies in their oral fluids. The antibody levels declined significantly after the second dose, but subsequently the rate of decline was slower.
CONCLUSIONS:
A high rate of seropositivity was found 20 years after the first MMR dose, particularly for rubella and measles. Our results show that MMR vaccine-induced antibodies wane significantly after the second dose. According to epidemiological data, the protection induced by MMR vaccination in Finland seems to persist at least until early adulthood. However, the situation requires constant vigilance.

Dine MS, et al., Persistence of vaccine-induced antibody to measles 26-33 years after vaccination. J Infect Dis. 2004 May 1;189 Suppl 1:S123–30.

Because measles-specific antibody titer after vaccination is lower than after natural infection, there is concern that vaccinated persons may gradually lose protection from measles. To examine the persistence of vaccine-induced antibody, participants of a vaccine study in 1971, with documentation of antibody 1-7 years after vaccination, were followed up in 1997-1999 to determine the presence and titer of measles antibody. Of the 56 participants (77% were 2-dose recipients), all had antibodies detected by the plaque reduction neutralization (PRN) antibody assay an average of 26-33 years after the first or second dose of measles vaccine; 92% had a PRN titer considered protective (>1 : 120). Baseline hemagglutination inhibition antibody titer in 1971 strongly predicted follow-up PRN antibody titer (P<.001). Persistence of antibody in these primarily 2-dose recipients supports the current elimination strategy to achieve and sustain high population immunity with a 2-dose schedule.

Paunio M et al. IgG avidity to distinguish secondary from primary measles vaccination failures: prospects for a more effective global measles elimination strategy. Expert Opinion on Pharmacotherapy. 2003;4:1215–1225.

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.

Pannuti CS, et al. Identification of primary and secondary measles vaccine failures by measurement of immunoglobulin G avidity in measles cases during the 1997 São Paulo epidemic. Clinical and Diagnostic Laboratory Immunology. 2004;11:119–122.

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.

GRADE table III: Duration of protection following measles immunization. http://www.who.int/immunization/measles_grad_duration.pdf?ua=1, accessed January 2017.

(No abstract available.)

WHO. Information Sheet. Observed rate of vaccine reactions – measles, mumps and rubella vaccines, May 2014. http://www.who.int/vaccine_safety/initiative/tools/MMR_vaccine_rates_information_sheet.pdf?ua=1, accessed December 2016.

(No abstract available.)

GRADE table IV: Safety of measles vaccine in young children and adolescents. http://www.who.int/immunization/documents/measles_grad_safety.pdf?ua=1, accessed January 2017.

(No abstract available.)

What clinicians need to know about MMRV vaccine safety. Atlanta, US Centers for Disease Control and Prevention. http://www.cdc.gov/vaccinesafety/vsd/mmrv.htm, accessed April 2017.

As part of routine safety monitoring for new vaccines, in 2007 CDC implemented a postlicensure vaccine safety study for the combined MMRV vaccine in children aged 12–23 months, the age when the first dose of MMRV or MMR and varicella vaccines is recommended.
Preliminary results from CDC's MMRV vaccine safety study among children aged 12–23 months found— The rate of febrile seizures during the 7–10 days after vaccination was about 2 times higher in children who received MMRV vaccine (9 per 10,000 children vaccinated), compared with children who received measles, mumps, and rubella (MMR) and varicella vaccines separately at the same visit (4 per 10,000 children vaccinated). During the 7–10 days after vaccination, about one additional febrile seizure would be expected to occur among every 2,000 children vaccinated with MMRV vaccine, compared with children vaccinated with MMR and varicella vaccine administered at the same visit. CDC, FDA, and ACIP continue to evaluate these preliminary findings and other relevant data. They will communicate updates and take any further necessary actions based on this evaluation.

Schink T et al., Risk of febrile convulsions after MMRV vaccination in comparison to MMR or MMR+V vaccination. Vaccine. 2014 Feb 3;32(6):645-50.

BACKGROUND:
In July 2006, Priorix-Tetra™, a combined measles-mumps-rubella-varicella (MMRV) vaccine, was licensed in Germany. Since a postlicensure study had shown a more than twofold elevated risk of febrile convulsions (FC) after first dose vaccination with the combined MMRV vaccine ProQuad(®) compared to separately administered MMR and V vaccines (MMR+V), the Paul-Ehrlich-Institute, the German regulatory agency for vaccine licensing and safety, requested a study investigating the risk of FC for Priorix-Tetra™.
METHODS:
We performed a matched cohort study based on claims data of more than 17 million insurees in the German Pharmacoepidemiological Research Database. All children born between 01.01.2004 and 31.12.2008 who received a 1st dose of MMRV vaccine were matched to children vaccinated with MMR, MMR+V and MMR or MMR+V (combined group), respectively, by sex, age, month of vaccination and statutory health insurance. The primary outcome was defined as hospitalization with a diagnosis of FC without any alternative plausible cause of FC, e.g. an infection or neurological condition, coded as main discharge diagnosis. The secondary outcome excluded only neurological conditions to provide a more comparable outcome definition to the one used in the ProQuad(®) study. Numbers needed to harm (NNH), risk ratios and confounder adjusted odds ratios (ORs) with 95% CIs were estimated to compare the exposure groups.
RESULTS:
In the main risk period 5-12 days after immunization, the adjusted ORs of the primary endpoint for immunization with MMRV vaccine relative to the comparator vaccine indicated in brackets were 4.1 [95% CI 1.3-12.7; MMR], 3.5 [0.7-19.0; MMR+V], and 4.1 [1.5-11.1; MMR and MMR+V]. The corresponding ORs for the secondary outcome were 2.3 [1.4-3.9; MMR], 1.5 [0.8-2.9; MMR+V] and 2.4 [1.5-3.9; MMR and MMR+V].
CONCLUSIONS:
This study in children younger than 5 years, 90% of them between 11 and 23 months, shows a risk of FC similar in magnitude for Priorix-Tetra™ as has previously been reported for ProQuad(®) suggesting a class effect for these quadrivalent vaccines.

Angel, JB et al., Vaccine-associated measles pneumonitis in an adult with AIDS. Ann. Intern. Med. 1998;129:104-106.

(No abstract available.)

Scott P et al., Measles Vaccination in HIV-Infected Children: Systematic Review and Meta-Analysis of Safety and Immunogenicity. Oxford Journals Medicine & Health The Journal of Infectious Diseases. Volume 204, Issue suppl 1.pp. S164-S178.

BACKGROUND:
Measles control may be more challenging in regions with a high prevalence of HIV infection. HIV-infected children are likely to derive particular benefit from measles vaccines because of an increased risk of severe illness. However, HIV infection can impair vaccine effectiveness and may increase the risk of serious adverse events after receipt of live vaccines. We conducted a systematic review to assess the safety and immunogenicity of measles vaccine in HIV-infected children.
METHODS:
The authors searched 8 databases through 12 February 2009 and reference lists. Study selection and data extraction were conducted in duplicate. Meta-analysis was conducted when appropriate.
RESULTS:

Thirty-nine studies published from 1987 through 2008 were included. In 19 studies with information about measles vaccine safety, more than half reported no serious adverse events. Among HIV-infected children, 59% (95% confidence intervals [CI], 46-71%) were seropositive after receiving standard-titer measles vaccine at 6 months (1 study), comparable to the proportion of seropositive HIV-infected children vaccinated at 9 (8 studies) and 12 months (10 studies). Among HIV-exposed but uninfected and HIV-unexposed children, the proportion of seropositive children increased with increasing age at vaccination. Fewer HIV-infected children were protected after vaccination at 12 months than HIV-exposed but uninfected children (relative risk, 0.61; 95% CI, .50-.73).
CONCLUSIONS:
Measles vaccines appear to be safe in HIV-infected children, but the evidence is limited. When the burden of measles is high, measles vaccination at 6 months of age is likely to benefit children of HIV-infected women, regardless of the child's HIV infection status.

WEEKLY EPIDEMIOLOGICAL RECORD, NO. 32, 7 AUGUST 2009, 84, pp. 325-332. Global Advisory Committee on Vaccine Safety, report of meeting held 17–18 June 2009.

(No abstract available.)

GRADE table V: Measles revaccination of HIV-infected children receiving highly active antiretroviral therapy. http://www.who.int/immunization/measles_grad_HIV.pdf?ua=1, accessed April 2017.

(No abstract available.)

WEEKLY EPIDEMIOLOGICAL RECORD, NO. 29, 19 JULY 2013, 88, pp. 301-312. Global Advisory Committee on Vaccine Safety, 12–13 June 2013.

(No abstract available.)

Sukumaran L et al., Adverse Events Following Measles, Mumps, and Rubella Vaccine in Adults Reported to the Vaccine Adverse Event Reporting System (VAERS). 2003–2013. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America. 2015 May 15;60(10):e58.

BACKGROUND:
Limited data exist on the safety of the measles, mumps, and rubella (MMR) vaccine in adults. We reviewed reports of adverse events (AEs) to the Vaccine Adverse Event Reporting System (VAERS) to assess safety in this previously understudied group.
METHODS:
VAERS is the national spontaneous vaccine safety surveillance system coadministered by the Centers for Disease Control and Prevention and the US Food and Drug Administration. We searched the VAERS database for US reports of adults aged ≥19 years who received the MMR vaccine from 1 January 2003 to 31 July 2013. We clinically reviewed reports and available medical records for serious AEs, pregnancy reports, and reports for selected prespecified outcomes.
RESULTS:
During this period, VAERS received 3175 US reports after MMR vaccine in adults. Of these, 168 (5%) were classified as serious, including 7 reports of death. Females accounted for 77% of reports. The most common signs and symptoms for all reports were pyrexia (19%), rash (17%), pain (13%), and arthralgia (13%). We did not detect any new safety findings in empirical Bayesian data mining. We

identified 131 reports of MMR vaccine administered to a pregnant woman; the majority of these vaccinations were in the first trimester and in 83 (62%), no AE was reported.
CONCLUSIONS:
In our review of VAERS data, we did not detect any new or unexpected safety concerns for MMR vaccination in adults. We identified reports of pregnant women exposed to MMR, which is a group in whom the vaccine is contraindicated, suggesting the need for continued provider education on vaccine recommendations and screening.

J. Gao et al., Epidemic of measles following the nationwide mass immunization campaign. BMC Infectious Diseases. 2013; 13: 139.

BACKGROUND:
A prolonged measles epidemic occurred in Wenzhou City, China after a nationwide measles mass immunization campaign (MMIC) in 2010. We conducted an investigation to identify factors contributing to this epidemic and to provide evidence-based recommendations for measles elimination strategies in China.
METHODS:
Measles was diagnosed using the national standard case-definitions. We estimated the population vaccination coverage based on the proportion of measles patients that had been vaccinated. In a case-control investigation, all measles patients who received treatment in The Second Affiliated Hospital of Wenzhou Medical College (Hospital S) during November 1 to December 31, 2010 served as cases; controls were randomly selected among all other patients who received treatment in Hospital S during the same time period, frequency matched by month of hospital visit. We reviewed medical records of case- and control-patients to compare their exposure history at Hospital S and to its intravenous rehydration room (IV room) during the incubation period (7-21 days before their illness onset).
RESULTS:
The attack rate of measles in Wenzhou City was 3.3/100,000 during September 1, 2010 to January 11, 2011. Children aged 8-11 m had the highest attack rate (171/100,000) of all age groups. In children not age-eligible for the MMIC but should have been routinely vaccinated after the MMIC, the vaccination rate was only 52%. In the case-control investigation, 60% (25/42) of case-patients compared with 21% (35/168) of control-patients had visited Hospital S (adjusted ORM-H = 5.5, 95% CI = 2.7-11). Among unvaccinated children who had received treatment in Hospital S, 84% (21/25) of case-patients compared 38% (11/29) of control-patients had visited the IV room (adjusted ORM-H = 9.2, 95% CI = 1.5-59).
CONCLUSION:
Relaxed routine measles vaccination among children after the MMIC was the main factor responsible for this epidemic. Exposure in the IV room at Hospital S facilitated the epidemic. To reach the goal of measles elimination, the Chinese public health authorities should make greater efforts to improve timely routine measles vaccination, and to reduce nosocomial transmission.

Zepp F et al. 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. European Journal of Pediatrics. 2007;166:857–864.

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-Haemophilusinfluenzae 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.

Vesikari T et al. Safety and immunogenicity of a booster dose of the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine co-administered with measles-mumps-rubella-varicella vaccine in children aged 12 to 16 months. Pediatr Infect Dis J. 2010 Jun;29(6):e47–56.

Background: A booster dose of pneumococcal conjugate vaccine may be administered at the same age as measles-mumps-rubella-varicella (MMRV) vaccination. This study examined the safety, reactogenicity, and immunogenicity of a booster dose of the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) when coadministered with MMRV vaccine.
Methods: In this open, controlled study, 325 healthy children aged 12 to 14 months were randomized to 1 of 3 groups: the first group (N = 110) received PHiD-CV and MMRV vaccine followed 6 to 8 weeks later by MMRV and DTPa-HBV-IPV/Hib vaccines; the second group (N = 101) received DTPa-HBV-IPV/Hib and MMRV vaccines followed 6 to 8 weeks later by PHiD-CV and MMRV vaccine; the third group (N = 114) received PHiD-CV and DTPa-HBV-IPV/Hib vaccine during 1 vaccination visit. Immune responses were assessed with GlaxoSmithKline's 22F-inhibition enzyme-linked immunosorbent assay (for PHiD-CV), commercial enzyme-linked immunosorbent assay (for MMR), or indirect immunofluorescence assay (for varicella). Adverse events were recorded by the parents/guardians.
Results: After the first vaccination, 2 peaks in fever (rectal temperature ≥38°C) were observed; at days 0 to 2, related to PHiD-CV and DTPa-HBV-IPV/Hib vaccination, and at days 4 to 12, related to MMRV vaccination. Booster responses to pneumococcal antigens and protein D and seroconversion rates for all MMRV vaccine components were high.
Conclusions: PHiD-CV and MMRV vaccine can be coadministered without compromising the safety and immunogenicity profiles of either vaccine.

Huang L-M et al. Concomitant administration of live attenuated Japanese encephalitis chimeric virus vaccine (JE-CV) and measles, mumps, rubella (MMR) vaccine: randomized study in toddlers in Taiwan. Vaccine. 2014 Sep 15;32(41):5363–9.

BACKGROUND:
Japanese encephalitis (JE) is the most important cause of viral encephalitis in Asia.
METHODS:

In this randomized, open-label, multicenter trial in 550 children aged 12 to 18 months in Taiwan, children received one dose of JE-CV and one dose of MMR vaccine. Vaccines were either administered separately 6 weeks apart (Groups 'JE-CV' and 'MMR', named after which vaccine was given first), or concomitantly (Group 'Co-Ad'). JE neutralizing antibody titers were assessed using PRNT50. MMR antibody levels were determined by ELISA.
RESULTS:
All groups had low seroprotection/seropositivity rates (<10%) before vaccination for all antigens. Forty two days after vaccination, on either Study Day 42 or 84, seroconversion rates for all antigens were high in all groups, irrespective of the order of vaccinations. Seroconversion for JE ranged from 96.9% in Group Co-Ad on D42 to 100% in Group MMR. Non-inferiority was demonstrated for all analyses as the lower bound of the 95% CI of the difference in seroconversion rates between groups was above the pre-defined limit of -10.0%. The immune responses remained high for all antigens and well above the level of protection 12 months after vaccination in all groups. There were no safety concerns.
CONCLUSIONS:
JE-CV is safe and induces a strong protective immune response which persists over 1 year when co-administered with MMR vaccine.

Nascimento Silva JR et al., Mutual interference on the immune response to yellow fever vaccine and a combined vaccine against measles, mumps and rubella. Vaccine. 2011 Aug 26;29(37):6327–34.

A randomized trial was conducted to assess the immunogenicity and reactogenicity of yellow fever vaccines (YFV) given either simultaneously in separate injections, or 30 days or more after a combined measles-mumps-rubella (MMR) vaccine. Volunteers were also randomized to YFV produced from 17DD and WHO-17D-213 substrains. The study group comprised 1769 healthy 12-month-old children brought to health care centers in Brasilia for routine vaccination. The reactogenicity was of the type and frequency expected for the vaccines and no severe adverse event was associated to either vaccine. Seroconversion and seropositivity 30 days or more after vaccination against yellow fever was similar across groups defined by YFV substrain. Subjects injected YFV and MMR simultaneously had lower seroconversion rates--90% for rubella, 70% for yellow fever and 61% for mumps--compared with those vaccinated 30 days apart--97% for rubella, 87% for yellow fever and 71% for mumps. Seroconversion rates for measles were higher than 98% in both comparison groups. Geometric mean titers for rubella and for yellow fever were approximately three times higher among those who got the vaccines 30 days apart. For measles and mumps antibodies GMTs were similar across groups. MMR's interference in immune response of YFV and YFV's interference in immune response of rubella and mumps components of MMR had never been reported before but are consistent with previous observations from other live vaccines. These results may affect the recommendations regarding primary vaccination with yellow fever vaccine and MMR.

Thompson, K. M., & Odahowski, C. L. (2016). Systematic review of health economic analyses of measles and rubella immunization interventions. Risk Analysis, 36(7), 1297-1314.

Economic analyses for vaccine-preventable diseases provide important insights about the value of prevention. We reviewed the literature to identify all of the peer-reviewed, published economic analyses of interventions related to measles and rubella immunization options to assess the different types of analyses performed and characterize key insights. We searched PubMed, the Science Citation Index, and references from relevant articles for studies in English and found 67 analyses that reported primary data and quantitative estimates of benefit-cost or cost-effectiveness analyses for measles and/or rubella immunization interventions. We removed studies that we

characterized as cost-minimization analyses from this sample because they generally provide insights that focused on more optimal strategies to achieve the same health outcome. The 67 analyses we included demonstrate the large economic benefits associated with preventing measles and rubella infections using vaccines and the benefit of combining measles and rubella antigens into a formulation that saves the costs associated with injecting the vaccines separately. Despite the importance of population immunity and dynamic viral transmission, most of the analyses used static models to estimate cases prevented and characterize benefits, although the use of dynamic models continues to increase. Many of the analyses focused on characterizing the most significant adverse outcomes (e.g., mortality for measles, congenital rubella syndrome for rubella) and/or only direct costs, and the most complete analyses present data from high-income countries.

Acharya A et al., Cost-effectiveness of measles elimination in Latin America and the Caribbean: a prospective analysis. Vaccine. 2002 Sep 10;20:3332–3341.

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.

Pelletier et al., A benefit-cost analysis of two-dose measles immunization in Canada. Vaccine. 1998;16:989–996

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 compaign 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 outweight the costs of such a program under all scenarios.

Zhou F et al., An economic analysis of the current universal 2-dose measles-mumps-rubella vaccination program in the United States. International Journal of Infectious Diseases. 2004;189

Suppl 1:S131–145.

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.

Dayan GH et al., Cost-effectiveness of three different vaccination strategies against measles in Zambian children. Vaccine. 2004;22:475–484.

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 on 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.

Commission on Macroeconomics and Health. Macroeconomics and health: investing in health for economic development. Report of the Commission on Macroeconomics and Health. Geneva, World Health Organization, 2001. http://whqlibdoc.who.int/publications/2001/924154550x.pdf, accessed January 2017.

(No abstract available.)

Edejer TT et al., Cost effectiveness analysis of strategies for child health in developing countries. BMJ. 2005;331:1177.

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.

Fiedler JL et al.,The cost of Child Health Days: a case study of Ethiopia's Enhanced Outreach Strategy (EOS). Health Policy and Planning. 2008;23:222–233.

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.

Thompson, KM and Odahowski, CL. The costs and valuation of health impacts of measles and rubella risk management policies. Risk Anal. 2016 Jul;36(7):1357-82.

National and global health policymakers require good information about the costs and benefits of their investments in measles and rubella immunization programs. Building on our review of the existing measles and rubella health economics literature, we develop inputs for use in regional and global models of the expected future benefits and costs of vaccination, treatment, surveillance, and other global coordination activities. Given diversity in the world and limited data, we characterize the costs for countries according to the 2013 World Bank income levels using 2013 U.S. dollars (2013$US). We estimate that routine immunization and supplemental immunization activities will cost governments and donors over 2013$US 2.3 billion per year for the foreseeable future, with high-income countries accounting for 55% of the costs, to vaccinate global birth cohorts of approximately 134 million surviving infants and to protect the global population of over 7 billion people. We find significantly higher costs and health consequences of measles or rubella disease

than with vaccine use, with the expected disability-adjusted life year (DALY) loss for case of disease generally at least 100 times the loss per vaccine dose. To support estimates of the economic benefits of investments in measles and/or rubella elimination or control, we characterize the probabilities of various sequelae of measles and rubella infections and vaccine adverse events, the DALY inputs for health outcomes, and the associated treatment costs. Managing measles and rubella to achieve the existing and future regional measles and rubella goals and the objectives of the Global Vaccine Action Plan will require an ongoing commitment of financial resources that will prevent adverse health outcomes and save the associated treatment costs.

Ozawa S, et al., Return On Investment From Childhood Immunization In Low- And Middle-Income Countries, 2011-20. Health Aff (Millwood). 2016 Feb;35(2):199-207.

An analysis of return on investment can help policy makers support, optimize, and advocate for the expansion of immunization programs in the world's poorest countries. We assessed the return on investment associated with achieving projected coverage levels for vaccinations to prevent diseases related to ten antigens in ninety-four low- and middle-income countries during 2011-20, the Decade of Vaccines. We derived these estimates by using costs of vaccines, supply chains, and service delivery and their associated economic benefits. Based on the costs of illnesses averted, we estimated that projected immunizations will yield a net return about 16 times greater than costs over the decade (uncertainty range: 10-25). Using a full-income approach, which quantifies the value that people place on living longer and healthier lives, we found that net returns amounted to 44 times the costs (uncertainty range: 27-67). Across all antigens, net returns were greater than costs. But to realize the substantial positive return on investment from immunization programs, it is essential that governments and donors provide the requisite investments.

Evidence-to-recommendation table for measles vaccine. http://www.who.int/immunization/policy/position_papers/measles_evidence_recommendation.pdf, accessed April 2017.

(No abstract available.)

Planning and Implementing High-Quality Supplementary Immunization Activities for Injectable Vaccines Using an Example of Measles and Rubella Vaccines. Field Guide. http://www.who.int/immunization/diseases/measles/SIA-Field-Guide.pdf?ua=1, accessed January 2017.

(No abstract available.)

Evidence-to-recommendation table for revaccination of HIV infected. http://www.who.int/immunization/policy/position_papers/measles_evidence_recommendation_hiv.pdf, accessed April 2017.

(No abstract available.)

WEEKLY EPIDEMIOLOGICAL RECORD, NO. 9/10, 3 MARCH 2017, 92, pp. 97–105. Roadmap to elimination standard measles and rubella surveillance.

(No abstract available.)

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