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ABSTRACT

This article presents the World Health Organization's (WHO) recommendations on the use of measles vaccines excerpted from the WHO position paper on Measles vaccines: WHO position paper – April 2017, published in the Weekly Epidemiological Record [1]. This position paper replaces the 2009 WHO position paper on measles vaccines [2]. The position paper summarizes the most recent developments in the field of measles and includes removal of introduction criteria for the routine second dose of measles-containing vaccine (MCV2), guidance on when to vaccinate infants from 6 months of age, and guidance on re-vaccination of HIV-infected children receiving highly active anti-retroviral therapy (HAART).

Footnotes to this paper provide a number of core references including references to grading tables that assess the quality of the scientific evidence, and to the evidence-to-recommendation table. In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes; they summarize essential background information on diseases and vaccines, and conclude with WHO's current position on the use of vaccines in the global context. Recommendations on the use of measles vaccines were discussed by SAGE in November 2013,October 2015 and October 2016; evidence presented at these meetings can be accessed at: www.who.int/immunization/sage/meetings/2013/november/presentations_background_docs/en/, www.who.int/immunization/sage/meetings/2015/october/presentations_background_docs/en/ and www.who.int/immunization/sage/meetings/2016/october/presentations_background_docs/en/.

1. WHO position

Vaccination against measles is recommended for all susceptible children and adults. The available live attenuated measles vaccines are safe and effective, provide long-lasting protection, are inexpensive and may be used interchangeably within immunization programmes.

Reaching all children with 2 doses of measles-containing vaccine (MCV) should be the standard for all national immunization programmes. Countries aiming at measles elimination should achieve ≥95% coverage with both doses equitably to all children in every district.

In addition to the first routine dose of MCV (MCV1), all countries should include a second routine dose of MCV (MCV2) in their national vaccination schedules regardless of the level of MCV1 coverage [3]. The addition of MCV2 in the second year of life reduces the accumulation of susceptible children by immunizing those who did not respond to MCV1 or did not receive the first dose. This measure has the further advantages of lengthening the period between campaigns, helping to establish a routine well-child visit during the second year of life, and reducing the risk of outbreaks.

As the addition of routine MCV2 covers only a single birth cohort and it takes time to achieve high rates of population-wide coverage, countries conducting regular campaigns to achieve high population immunity should consider cessation of campaigns only when >90–95% vaccination coverage has been achieved at the national level for both MCV1 and MCV2, as determined by accurate coverage data for a period of at least 3 consecutive years.

1.1. Optimal timing for routine MCV1 and MCV2

In countries with ongoing transmission in which the risk of measles mortality among infants remains high, MCV1 should be administered at 9 months of age. In these settings, on-time delivery of MCV1 is important to ensure optimal protection during the susceptible period in infancy. These countries should administer the routine dose of MCV2 at age 15–18 months. The minimum interval between MCV1 and MCV2 is 4 weeks.

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In countries with low levels of measles transmission (i.e. those nearing measles elimination or verified as having eliminated endemic measles virus transmission) and therefore the risk of measles virus infection among infants is low, MCV1 may be administered at 12 months of age to take advantage of the higher seroconversion rates achieved at this age. Increasing the age of administration of MCV1 from 9 to 12 months represents a rational and desirable policy change. However, before implementing this change, policymakers should review local data on the age at which infants actually receive measles vaccine, the coverage expected at 12 months compared with 9 months, and the age-specific measles incidence.

In countries where MCV1 is administered at 12 months of age, the optimal age for delivering routine MCV2 is based on programmatic considerations that achieve the highest coverage of MCV2 and, hence, the highest population immunity. Administration of MCV2 at 15–18 months of age ensures early protection of the individual, slows the accumulation of susceptible young children, may correspond to the schedule for other routine immunizations (for example, a diphtheria-tetanus-pertussis vaccines (DTP) booster, pneumococcal conjugate vaccines (PCV), or meningococcal vaccines). This measure also supports the establishment of a policy on immunization and other health interventions in the second year of life. If MCV1 coverage is high (>90%) and school enrolment is high (>95%), administration of routine MCV2 at school entry may prove an effective strategy for achieving high coverage and preventing outbreaks in schools.

In the following situations, a supplementary dose of MCV should be given to infants from 6 months of age:

1. during a measles outbreak as part of intensified service delivery;
2. during campaigns in settings where the risk of measles among infants <9 months of age remains high (e.g. in endemic countries experiencing regular outbreaks);
3. for internally displaced populations and refugees, and populations in conflict zones;
4. for individual infants at high risk of contracting measles (e.g. contacts of known measles cases or in settings with increased risk of exposure during outbreaks such as day-care facilities);
5. for infants travelling to countries experiencing measles outbreaks;
6. for infants known to be human immunodeficiency virus (HIV)-infected or exposed (i.e. born to an HIV-infected woman).

Measles vaccine immunogenicity and effectiveness are lower at 6 months than at later ages, and there are concerns about the long-term effectiveness of an early 2-dose schedule and its potential for later blunting of immunity. MCV administered before 9 months of age should therefore be considered a supplementary dose and recorded on the child's vaccination record as "MCV0" unless the country has data showing high seroconversion when vaccination is carried out before 9 months of age. Children who receive a MCV0 dose should also receive MCV1 and MCV2 at the recommended ages according to the national schedule.

Available evidence on safety and immunogenicity of rubella and mumps-containing vaccines support their use from 6 months of age. Countries using measles–rubella (MR) vaccine or measles–mumps–rubella (MMR) vaccine in their national schedule should use the combined vaccine rather than measles-only formulations in all children, including those aged <1 year.

Because many cases of measles occur in children aged >12 months who have not been vaccinated, routine delivery of MCV1 should not be limited to infants aged 9–12 months and routine delivery of MCV2 should not be limited to infants aged 15–18 months of age. Every opportunity (e.g. whenever children come in contact with health services) should be taken to vaccinate all children who missed one or both MCV routine doses, particularly those <15 years of age. Policies prohibiting the use of the vaccine in children >1 year of age, older children and adolescents should be changed to allow them to be vaccinated as necessary.

Irrespective of the strategy or schedule, the child's immunization card and the clinic's vaccination register should be designed to allow accurate recording of supplementary (MCV0), routine (MCV1 and MCV2) and campaign doses. Children should be screened for their measles vaccination history at the time of school entry, and those lacking evidence of receipt of 2 doses should be vaccinated with any missing doses.

1.2. Vaccination campaigns

In countries where health systems are functioning only moderately or weakly, implementation of regular measles vaccination campaigns can be a highly effective strategy for protecting children who do not have access to routine health services, particularly if hard-to-reach communities are targeted during the campaign. At the community level, well planned and executed campaigns can rapidly increase population immunity and thereby interrupt measles virus transmission (i.e. achieve herd protection). Campaigns can also be used to close known immunity gaps (e.g. targeting individuals who were missed during historical vaccine stockouts or due to social disruptions). In certain settings, nationwide campaigns may not be feasible or cost-effective (e.g. due to civil unrest, political instability, financial constraints or in very large countries) and targeted subnational campaigns may be implemented to reduce the accumulation of susceptible individuals.

Because the risk of measles outbreaks is determined by the rate of accumulation of susceptible people in the population, programmes should use available good quality data on population immunity (i.e. vaccination coverage, surveillance, serological studies) to monitor the accumulation of susceptible people and conduct follow-up campaigns before the number of pre-school children susceptible to measles approaches the equivalent of one birth cohort, in order to prevent an outbreak of measles. This approach has been found to be programmatically useful in preventing large outbreaks. However, for large countries and countries which are close to measles elimination, a more extensive assessment of the accumulation of susceptible persons should be carried out at the subnational level.

As there is no single criterion for identification of the target age range for measles or measles/rubella vaccination campaigns, countries should integrate their surveillance, demographic, survey and seroprevalence data together with vaccination coverage information, history of MCV and rubella-containing vaccination (RCV) use, and local knowledge to determine the age distribution of susceptibility (age-specific immunity gaps) and hence the target age range/s for measles and MR campaigns. Additional information to consider relative to MR campaigns is rubella immunity among women of child-bearing age, the epidemiology of rubella and congenital rubella syndrome (CRS), age-specific fertility rates, and the age of mothers of CRS-affected infants. Mathematical modelling suggests a high quality measles campaign (reaching >90% of susceptible children) targeting children aged <5 years is equally effective and more cost-efficient than a lower quality wider age range campaign (e.g. targeting children aged <10 years reaching >70% of susceptible children) [4].

All MCV campaigns should follow established best practices, should be monitored to ensure readiness before the campaign, and be independently monitored during and after the campaign to ensure homogeneous vaccination coverage of >95% [5]. All doses given during campaigns should be documented in the child's vaccination record and the number of zero-dose children vaccinated (i.e. children who had not received any previous doses of MCV) recorded by age group.

Before discontinuing campaigns, a review should be conducted by a national committee such as the national immunization advisory

group. The committee should examine the following: historical data on vaccination coverage for MCV1, routine MCV2 and campaigns both at the national and district levels[1]; degree of heterogeneity of routine coverage among districts; population immunity profile; predicted rate of accumulation of susceptible individuals in the absence of campaigns; detailed epidemiology of measles including measles outbreaks; and the performance of the measles surveillance system. In the absence of adequate data, or if data suggest that cessation of campaigns would allow population immunity to drop below the herd immunity threshold, campaigns should continue.

Ensuring that every child is vaccinated with 2 doses of measles vaccine will require increased investment in systems to record and monitor the administration of both doses, including when they are delivered through campaigns.

1.3. Choice of vaccines and their interchangeability

All commercially available live attenuated measles vaccines, either as monovalent vaccine or in combination with rubella, mumps, or varicella vaccines, or some combination of these, can be used interchangeably to protect against measles. However, for programmatic reasons (e.g. to reduce cold storage needs and vaccine wastage), it is recommended that the same formulation is used for both routine doses of MCV.

1.4. Co-administration

As a general rule, live vaccines should be given either simultaneously or at intervals of 4 weeks. An exception to this rule is oral poliovirus vaccine, which can be given at any time before or after measles vaccination without interference in the response to either vaccine. MCVs may be co-administered at different anatomical sites with other vaccines including Japanese encephalitis vaccine, yellow fever vaccine, DTP-containing vaccines, meningococcal vaccine, hepatitis B vaccine, inactivated poliovirus vaccine, *Haemophilus influenza* type b conjugate vaccine, and PCV.

1.5. Contraindications

MCVs should not be given to individuals with a history of anaphylactic reactions or severe allergic reactions to any component of the vaccine (e.g. neomycin or gelatin) or those with any form of severe immunosuppression. Mild concurrent infections are not a contraindication to vaccination.

1.5.1. Vaccination of pregnant women

As a precautionary measure, measles vaccine – alone or in combination with other vaccines – should be avoided during pregnancy. No significant adverse outcomes for fetus or mother following vaccination of pregnant women have been reported. Inadvertent administration of measles vaccine during pregnancy is not a reason for terminating the pregnancy.

1.5.2. Vaccination of health-care workers (HCWs)

Because of the known risk of spreading measles from HCWs to patients or from patients to HCWs, all HCWs[2] and any staff who are in contact with patients should be immune to measles.[3] Verification of vaccination and/or history of measles should be integrated into standard infection control guidelines or other standards of care for health-care workers. For HCWs who have contact with patients, documentation of immunity should be required before signing an employment contract or entering into a training programme.

1.6. Vaccination of travellers

Susceptible individuals travelling to measles-endemic areas are considered at risk of contracting measles. Vaccine should be offered to children from 6 months of age, adolescents and adults likely or known to be susceptible.

1.7. Measles vaccination of HIV-infected individuals

Given the severe course of measles in patients with Acquired Immune Deficiency Syndrome (AIDS), measles vaccination should be routinely administered to potentially susceptible, asymptomatic HIV-infected children and adults. Vaccination may even be considered for those with symptomatic HIV infection if they are not severely immunosuppressed according to conventional definitions. In areas where there is a high incidence of both HIV infection and measles, an initial dose of MCV may be offered as early as age 6 months (recorded as MCV0). The 2 routine doses of MCV (MCV1 and MCV2) should then be administered to these children according to the national immunization schedule.

HIV-infected children vaccinated prior to the initiation of highly active antiretroviral treatment (HAART) are at increased risk of measles because of poor antibody responses following vaccination. While HAART does not restore measles immunity acquired after previous vaccine doses, it enables higher and more prolonged antibody responses following revaccination.

An additional dose of MCV should be administered to HIV-infected children receiving HAART following immune reconstitution [6]. If $CD4^+$T lymphocyte counts are monitored, an additional dose of MCV should be administered when immune reconstitution has been achieved, e.g. when the $CD4^+$ T lymphocyte count reaches 20–25%. Where $CD4^+$ T lymphocyte monitoring is not available, children should receive an additional dose of MCV 6–12 months after initiation of HAART. Current evidence is insufficient to recommend an additional dose for children who start HAART prior to the first dose of MCV.

A supplementary dose of MCV (recorded as MCV0) should be considered for infants known to be exposed (i.e. born to an HIV-infected woman) or soon after diagnosis of HIV infection in children older than 6 months who are not receiving HAART and for whom the risk of measles is high, with the aim of providing partial protection until they are revaccinated after immune reconstitution with HAART.

1.8. Surveillance and outbreak response

High quality measles case-based surveillance is a critical strategy for measles control and elimination. As countries approach elimination, they should intensify surveillance and move towards weekly reporting to the WHO regional offices [7]. Countries are encouraged to adopt the approach outlined in the framework for verification of measles and rubella elimination [8]. To limit the impact of measles outbreaks, WHO recommends surveillance for early detection, thorough assessment of the risk of spread and of severe disease outcomes, identification of immunity gaps, and planning rapid responses, including expanded use of MCVs.

A district or regional outbreak coordination committee with broad representation should make the decisions about the type of vaccination response to be implemented at the local level. To protect individuals at high risk during an outbreak, vaccination within 72 h of exposure may be given to modify the clinical course of measles or prevent symptoms. In individuals for whom

[1] A district is defined as the third administrative level in a country.

[2] All persons involved in patient care such as health care professionals, residents, students, laboratory staff, as well as persons in public health such as field workers, epidemiologists, laboratory staff and community health-care workers.

[3] Either written documentation of receipt of 2 doses of MCV and at least 1 dose of RCV or positive serologic (IgG) test results from a proficient laboratory.

vaccination is contraindicated, the administration of measles immune globulin within 6 days of exposure may have a similarly beneficial effect.

When determining whether a country or the WHO Region as a whole has achieved elimination, the regional verification commission should consider 5 lines of evidence – disease epidemiology, population immunity, quality of surveillance, sustainability of the programme, and genotyping evidence – to allow for a comprehensive evidence-based assessment of past programme performance and future capacity to sustain elimination. These lines of evidence should be evaluated together to establish the case for elimination.

1.9. Recommendations on selected research needs

Research is necessary to identify gaps in essential evidence and programme barriers to achieving measles and rubella/CRS elimination. Advances of major importance are in development, of which the most significant are likely to be administration of measles vaccine through microarray patches, and point-of-care diagnostic tests. Microarray patches would allow house-to-house vaccination and allow non-medically trained personnel to administer vaccine, which would be of great benefit for countries with limited human resources. Such innovations would increase the likelihood of success in reaching regional elimination goals.

Operational research can assist in appropriately guiding the implementation of programmatic strategies and the tailoring of approaches to local contexts. Programmatic questions that should be addressed include: which populations should be targeted for special immunization efforts; optimal strategies for reaching hard-to-reach populations, and adolescents and adults; how to strengthen and enhance disease surveillance and reporting; the best approaches to measuring vaccination coverage; strategies to communicate the benefits of measles vaccination and minimize vaccine hesitancy; and the economic impact of the disease. Research targeting programmatic challenges is likely to yield the most programmatic gains and should be prioritized.

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