Background
At its April 2006 meeting, SAGE noted the remarkable progress made towards the 2005 global measles mortality reduction goal and commended countries and the Measles Partnership for their combined achievements. Provisional estimates for 2005 indicate global measles deaths have been reduced by 60% compared with baseline level in 1999 (873,000 deaths). In view of the fact that it will be more challenging to fully implement measles mortality reduction strategies in large countries that have not yet implemented catch-up campaigns, SAGE considered that the GIVS goal of 90% mortality reduction by 2010 remained appropriate. SAGE recommended that work be undertaken to prepare for discussions on the feasibility of a global elimination goal.

SAGE noted the lessons learnt in the African Region where, despite successful measles catch-up campaigns and substantial reductions in measles mortality, outbreaks continue to happen. SAGE concluded that measles mortality reduction strategies need further adaptation and recommended that a working group be established to address the technical issues surrounding implementation of such strategies and report back to the November 2006 meeting.

Meeting Proceedings
The first meeting on the SAGE Working Group on Measles (WGM) was held on 28th September 2006 at WHO Headquarters in Geneva, Switzerland. The meeting agenda and list of participants (including members of the working group) can be found in annexes 1 and 2, respectively.

The objective of the meeting was to review country experience with implementation of the measles mortality reduction strategies and make recommendations for adjusting current immunization strategies. Specifically the working group was asked to address the following questions:

1. Under what circumstances should countries increase the age of administration of the 1st dose of measles vaccine from 9 months to 12 months?
2. Under what circumstances should countries add a second dose of measles vaccine to their routine childhood immunization schedule?
3. What is the optimal time interval between measles supplementary immunization activities?

The meeting was opened by the chairperson, Professor Hyam Bashour, who outlined the reason for establishing the working group and the objectives of the first meeting. Dr. Philippe Duclos, Executive Secretary of the SAGE, explained the direct linkage between the working group and the SAGE itself and that any recommendations from the group would be presented and discussed by the SAGE at their meeting on 20-22 November 2006. Dr. Stephen Cochi acted as rapporteur for the meeting.
Technical presentations
Two technical presentations on the immunological basis for measles immunization and the effects of changing the immunization schedule on population immunity were made by Dr Moss and Dr De Serres, respectively. The following paragraphs summarize these two presentations.

Dr. Moss provided a comprehensive review of the immune response to wild measles virus infection noting that immunological memory to measles is long lasting (even in the absence of re-exposure) and generally life-long and involves a combination of both humoral and cell mediated immunity. Whereas the presence of circulating neutralizing antibody (some studies defining this as $\geq 120$ mIU/mL) is sufficient to prevent measles infection and disease, cell mediated immunity is required to clear virus once infection has occurred. Antibody and cellular responses following vaccination with a live attenuated virus are qualitatively similar but of lesser magnitude than those following infection with wild type virus. Although duration of protection may be less after vaccination, it appears to be life-long in most vaccine recipients and waning immunity does not appear to be an important source of susceptibility at the population level.

Factors affecting the immune response to measles vaccine include: age at vaccination, immune suppressive conditions, intercurrent illness, nutritional status, host genetic factors, and strain of measles vaccine virus. Of these, age at vaccination is the most important which in turn is dependent on the level of maternal antibodies (lower in vaccinated vs. naturally infected mothers) and immaturity of the immune system among infants $\leq 6$ months of age. The graph below shows the relationship between age at vaccination and the proportion of children who seroconvert based on a review of 65 published studies. At 9 months of age, the median proportion of children responding was 90% (IQR: 82-95), whereas at $>12$ months the response rate was 96% (IQR: 88-100). However, the wide variations in the study designs, in particular the varying definitions for seroresponse, limit the interpretation of these data.
A recent study in Zambia found HIV-infection in mothers was associated with more rapid loss of maternal antibody in their infants. Whereas neutralizing antibody titres were similar in HIV-infected and non-infected infants following vaccination, by 27 months post-vaccination, a significant proportion of HIV-infected children had become seronegative suggesting possible waning of protection. In the absence of treatment, most of HIV-infected children die in early childhood and hence do not play a major role in measles transmission. This situation is changing with increasing use of anti-retroviral therapies and these children may benefit from a second dose of measles vaccine.

Neutralizing Antibodies to Measles Virus Among HIV-Infected and Uninfected Children

As described originally by Halsey et al., the optimal age for measles vaccination is a trade-off between the probability of developing an immune response (related to the rate of decline in maternal antibodies) and the average age of infection.
Over 95% of children who fail to respond to their first dose of measles vaccine, respond to a second dose. This occurs even among children with certain HLA class I and class II alleles associated with lack of response to the first dose. Hence a second opportunity for measles immunization serves to protect children who either failed to respond to their 1st dose or missed getting vaccinated with the 1st dose. Work is being done on alternative routes of delivery of existing measles vaccines (e.g., via aerosol) and novel vaccines that may be able to induce immunity in early infancy (e.g., DNA vaccines, expression vectors, and alphavirus replicons). However, these approaches are unlikely to yield a licensed product before 2010 and measles control activities will continue to rely on existing live attenuated measles vaccines in the immediate future.

Dr. De Serres in his presentation on the effects of changing the immunization schedule on population immunity, noted that the optimal age for vaccination seeks to maximize the immunity in the population while minimizing the number of cases and deaths occurring both before and after the age at vaccination. He presented a model based on the following assumptions: a high force of infection resulting in a relatively high proportion of cases occurring before 12 months of age; age-specific case-fatality ratios similar to those observed during an outbreak in Niger in 2003; and a gradient of improved protection with increasing age at vaccination (>5% increase in vaccine effectiveness at 12 vs. 9 months). The following 2 graphs indicate the effect of shifting the dose of measles vaccine from 9 months to 12 months of age under these model assumptions. Although a dose at 12 months results in a higher proportion of remaining cases in the <1 year age group, the overall population immunity is higher resulting in fewer measles cases and a lower number of measles deaths overall. This effect was even more marked if the force of infection was lower (e.g., after an SIA).
He concluded that the age of vaccination should be increased from 9 to 12 months of age because of the higher vaccine effectiveness obtained at 12 months and the effect this has on overall population immunity. In particular, this approach should be introduced after a successful catch-up campaign when the force of infection has been substantially reduced thereby reducing the risk of disease among infants (i.e., prior to vaccination age) and if high routine vaccination coverage can be sustained post SIA. This favourable epidemiological situation is enhanced if a block of neighbouring countries have all conducted catch-up campaigns in the recent past thereby reducing the risk of importation. However, it should be emphasized that this is based on the
model assumptions used. The issue of raising the age of routine vaccination should also be based on country-specific measles incidence, case-fatality ratios, and age-specific responses to vaccination.

**Questions for discussion**

**Question 1.**

Dr. Dabbagh introduced the discussion on the question: *Under what circumstances should countries increase the age of the 1st dose from 9 months to 12 months?*. She made the following key points in her presentation:

- 40% of the 192 WHO member states recommend measles containing vaccine at 9 months - mainly in the African and SE Asian regions, highlighting the point that the above question mainly concerns these 2 regions that have a mortality reduction goal.

- The WHO publication *Immunological Basis for Measles Immunization* is outdated (1993) and is not aligned with the current WHO/UNICEF recommended strategies for measles control. In addition, the WHO position paper on measles (2004) provides no guidance on the question of whether and when countries should change the age of the first dose of measles vaccine.

- Programmatic considerations that should be taken into account include the actual age of administration, possible decreases in coverage with advancing age (increasing drop out rate), the impact of changing the schedule on other health interventions given at 9 months of age (e.g. yellow fever vaccine, Japanese encephalitis vaccine and vitamin A).

- Limited data are available on actual time of vaccination. A recent study (2006) in Australia demonstrated that 26% of children receiving MMR received it with more than one month delay, with delays more likely among children with indigenous status. In addition, timeliness of vaccination worsened with increasing age at vaccination.

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![Age for administering MCV1 in Immunization Schedule](chart.png)

Data source, JRF 2005
In April 2005, the Technical Advisory Group on Measles for the African Region (AFRO Measles TAG) decided to keep the recommended age for the 1st dose of measles vaccine at 9 months. They requested more information from African countries on the following factors: the actual age of vaccination with the 1st dose; the age and vaccination status of measles cases following SIAs; factors affecting seroconversion rates (e.g., HIV infection); and local data on age-specific seroconversion at 6, 9, and 12 months of age.

**Discussion and recommendations**

The updated review of the literature suggests that measles vaccine effectiveness is approximately 90% at 9m and increases to ≥95% at 12m. In countries where measles transmission is still widespread (e.g., prior to catch-up campaign) and the force of infection during infancy is high, the recommended age for administration of the 1st dose of measles remains at 9 months of age or as soon as possible thereafter.

In some countries, current practice considers measles vaccination to be only indicated for infants aged 9-12 months. This results in missed opportunities for vaccination of children aged ≥12 months who present to the health services for any reason. In addition to routine vaccination of infants ages 9-11 months, measles vaccine should be administered to any child aged ≥12 months (up to age 15 years\(^1\)) who lacks evidence of receipt of at least 1 dose of measles vaccine administered at ≥9 months of age. A dose of measles vaccine administered at <9 months of age should not count as a valid dose. For such children an additional dose of vaccine should be administered at ≥9 months of age and at least 4 weeks (28 days) after the initial dose.

The participants discussed the issues of accumulation of susceptibles, the role of SIAs in reducing the burden of disease, the experiences in different regions, integration with other health interventions, the problems of deciding age of vaccination, the lack of data on disease incidence, etc. Experiences from PAHO and EURO regions were highlighted, where individual countries rather than the region as a whole shifted the age of first vaccination.

The SAGE WGM believed that, based on the data presented, increasing the age of routine administration of the 1st dose of measles vaccine from 9 to 12 months of age represents a rational and desirable policy change that countries should begin to consider. However, they were not ready to recommend this strategy for general implementation before reviewing recent data from developing countries (especially Africa) on the set of factors listed below (particularly #3, 4, and 5).

The SAGE WGM recommended that countries planning nationwide measles SIAs (i.e., catch-up or follow-up campaigns) evaluate the following conditions to enable an informed decision of whether to increase the routine age for measles vaccination from 9 to 12 months:

1. Expected level of population immunity following the SIA which in turn depends on the coverage achieved during in the SIA as well as routine vaccination coverage following the SIA.
2. The actual age at which infants receive measles vaccine

\(^1\) In large countries or settings where vaccine availability may be limited, going up to 5 years of age may be more practical.
3. The immunization coverage expected to be achieved at 12 months of age as compared to 9 months of age
4. Information from local studies of the immunogenicity and/or vaccine effectiveness of measles vaccine administered at 9 vs. 12 months of age.
5. Data on the age-specific incidence of measles
6. Other interventions given at the well child visit at 9 months of age (e.g., vitamin A, yellow fever vaccine, JE vaccine) and decide whether it would be best to delay other interventions or maintain the 9 month visit for the other interventions and add an additional visit at 12 months for measles vaccination.

Further, the WGM noted that the WHO document on the Immunological Basis for Measles Immunization is outdated and recommended an updated version to be prepared. They also advised that data from measles surveillance as well as vaccine coverage needs to be collected and compiled for countries to take the decision in due time.

**Question 2.**
Ms Goodman introduced the question: *Under what circumstances should countries add a 2nd dose of measles vaccine in their routine childhood immunization schedule?*

Key points from her presentation included:
- Current WHO recommendations lack specific guidance on when and how to introduce a routine 2nd dose
- An analysis of global use of a routine 2-dose measles vaccination schedule shows that this is occurring in 126/192 countries; predominantly industrialized countries with a measles elimination goal.

### Analysis of the 2-dose Schedules and Age of Vaccination
*(WHO/UNICEF JRF 2005)*

<table>
<thead>
<tr>
<th>2 dose schedule</th>
<th>AFRO (6/46)</th>
<th>SEARO (3/11)</th>
<th>WPRO (15/27)</th>
<th>EMRO (18/21)</th>
<th>AMRO (28/35)</th>
<th>EURO (52/52)</th>
<th>Total (126/192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 9 months + 9-12 months</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>9 months + 15-18 months</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>12 months + 13-24 months</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>21</td>
<td>32</td>
</tr>
<tr>
<td>12-15 months + 3-6 years</td>
<td>3</td>
<td>5</td>
<td>0</td>
<td>8</td>
<td>21</td>
<td>32</td>
<td>72</td>
</tr>
<tr>
<td>12-15 months + 7-13 years</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>15</td>
<td>20</td>
</tr>
</tbody>
</table>

- Dijibouti (9 months + 24 months)
- Algeria, Morocco, Indonesia, Thailand (9 months + 6 years) and Sri Lanka (9 months + 3 years)
- Bosnia & Herzegovina (24 months + 6 years)

- Programmatic benefits of a routine 2nd dose include sustainability, potentially slower accumulation of susceptibles (allowing a longer interval between SIAs), and an additional opportunity for other child survival interventions
Cost-effectiveness analysis and model data support introduction particularly if high coverage can be achieved

GIVS encourages expanding use of vaccines beyond infancy and integration with other interventions

GAVI has made funds available for introduction of a routine 2nd dose if countries have DTP3 coverage >50% and provide evidence of WHO technical advice recommending introduction

Programmatic challenges to introduction of a routine 2nd dose include planning for additional vaccine supply and storage, cold chain logistics, staff training, revision of immunization cards/data collection forms, social mobilization, and health education for mothers

AFRO Measles TAG encouraged well performing programmes to apply for GAVI funds if they meet the following criteria: 1st dose measles coverage of >80% (with minimal heterogeneity); the Reaching Every District Strategy (RED) in place; and established case-based surveillance for measles.

Discussion and recommendations
To start the discussion the question was posed should criteria for introduction of a routine 2nd dose be set high (to maximize the disease control objective) or at a lower level recognizing individual benefit and the need to build systems (to meet a programme management objective)?

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2 GAVI Guidelines on Country Proposals for Support to New and Under-Used Vaccines, October 2006 (Final Draft): "GAVI will provide support for countries to introduce second dose measles vaccination into their routine immunization program, if this is included in the country’s cMYP or equivalent, and is not already supported through non-GAVI funding. All countries submitting applications for the introduction of routine second dose measles vaccine will be required to provide evidence of WHO’s technical advice recommending introduction in that country."
There was active debate on the issue of whether a routine 2nd dose should be recommended for all countries regardless of their disease control goal or strength of the routine programme. Some participants felt introduction of a well child visit in the 2nd year of life coupled with routine administration of a 2nd dose of measles would not only address primary measles vaccine failures but also led to improved coverage with other life-saving interventions (e.g., vitamin A, malaria prevention strategies). Other participants noted the results from modelling indicating that relatively high coverage needs to be achieved with the 2nd dose for it to be an effective disease control strategy. In addition, concerns were expressed that introduction of a routine 2nd dose in weaker immunization systems would divert resources away from more effective control measures such as increasing on-time 1st dose coverage and high quality follow-up SIAs.

In view of the GAVI funds that have been made available for introduction of a routine 2nd dose (13 million USD for countries in the African Region and an additional 8 million USD for countries outside Africa that is expected from the IFFIm) the discussion focused on the criteria for introduction as well as the recommended age of administration of the second dose.

The WGM supported the principle of the existing AFRO Measles TAG recommendation that countries should be encouraged to introduce a routine 2nd dose if they have a well functioning routine immunization programme. The following conditions should be met in order to maximize its effectiveness:

1. National level routine coverage with the 1st dose should be ≥75% (based on the most accurate measurement available, e.g., WHO/UNICEF best estimates)
2. The RED approach is in place to adequately sustain routine vaccination coverage in the weakest districts
3. Case-based measles surveillance that meets WHO performance indicators has been established
4. The routine 2nd dose, where appropriate, is administered together with other child survival interventions (e.g., vitamin A, deworming medicines, malaria control measures)
5. Technical consultation with WHO and UNICEF country and regional offices occurs prior to introduction

The WGM requested that country experiences with introduction of a routine 2nd dose be reviewed within 2 years to determine the impact on measles control and the delivery of immunizations and child health services as a whole.

The WGM noted the numerous examples of countries experiencing measles outbreaks because of delays in implementing follow-up SIAs. Follow-up SIAs, especially when combined with other interventions (e.g., vitamin A, deworming and ITN distribution) are a highly effective method for reaching children who have missed routine vaccination and preventing outbreaks. Countries should continue to conduct regular follow-up SIAs and only suspend them when the WHO/UNICEF best estimates of coverage with both routine doses reach >90% (NOTE: PAHO and WPRO have established a higher standard of >95% for their member countries) and surveillance is detecting ≥ 1 suspected case per 100,000 population in ≥ 80% of districts.
In large countries with heterogeneous coverage (e.g., India, Pakistan, Ethiopia, and Nigeria) consideration may be given to introducing a routine 2nd dose in those states/provinces that reach the coverage threshold and meet the other criteria as laid out above.

The 2nd dose should be given as soon as possible after the 1st dose allowing at least 1 month (28 days minimum) between doses. Because of programmatic considerations aimed at optimizing vaccination coverage, the age of administration of the routine 2nd dose may range from early in the 2nd year of life to school entry.

Question 3.
Dr. Strebel introduced the discussion on the question: *What is the optimal interval between SIAs?* He made the following key points in his presentation:

- Factors affecting the interval include: the rate at which susceptibles accumulate in the population; the occurrence of inter-campaign outbreaks; availability of funds; delays due to integration of other interventions (e.g., ITNs) and political pressure.
- The main technical factor is the rate of accumulation of susceptible children which in turn is a function of the coverage achieved in the preceding SIA and the routine coverage among subsequent birth cohorts.
- PAHO recommends conducting an SIA when the estimated number of measles-susceptible preschool age children approaches the size of the country birth cohort.

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**Optimal interval between measles SIAs based on mean routine immunization coverage**

![Optimal interval between measles SIAs based on mean routine immunization coverage](image)

Source: de Quadros et al. JAMA 275:224-9, 1996

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- A review of country experience in the Americas found approximately 60% of countries conducted campaigns on schedule and outbreaks tended to occur in countries that delayed their follow-up SIAs (e.g., Sao Paulo State in Brazil, Venezuela).
- The AFRO Measles TAG adopted similar guidelines to PAHO and so far most countries have been on schedule. The major difference is that more countries have low (<60%) or moderate (60-79%) routine coverage and this together with more...
importations from neighbouring countries (who have not yet conducted SIAs) has resulted in outbreaks before the next scheduled SIA (e.g., Uganda - see below)

Discussion and recommendations:

The following question was posed: "If the goal is mortality reduction, is it acceptable to have outbreaks before the next scheduled SIA?" Some participants felt that outbreaks are associated with mortality (e.g., the Kenyan outbreak in 2005) and that if the goal is near zero mortality then all outbreaks should be prevented. Others argued that this is equivalent to an elimination goal (which is not consistent with the mortality reduction goals in the African and SE Asian Regions) and hence small to moderate size outbreaks should be accepted as part of a mortality reduction strategy.

With respect to the interval between SIAs, the WGM agreed with the approach reflected in the PAHO Measles Field Guide and adapted by the AFRO Measles TAG and recommended the following:

- After measles SIAs that achieve relatively homogeneous\(^3\) coverage rates of  \(\geq 90\%\)
  - If routine measles coverage is  \(\geq 80\%\) - an interval of 4 years
  - If routine measles coverage is  \(\geq 60\%-79\%\) - an interval of 3 years
  - If routine measles coverage is  \(< 60\%\) - an interval of 2 years

- After measles SIAs that achieve relatively homogeneous coverage rates of  \(< 90\%\)
  - If routine measles coverage is  \(\geq 80\%\) - an interval of 3 years
  - If routine measles coverage is  \(< 80\%\) - an interval of 2 years

- After measles SIAs with relatively heterogeneous\(^4\) coverage rates or in large countries (e.g., India, Indonesia, and Nigeria) with variable SIA coverage (i.e., >10% between any two provinces/states)

\(^3\) Homogenous vaccine coverage:  <5% of districts with DTP3 coverage <50%

\(^4\) Heterogeneous vaccine coverage:  >5% of districts with DTP3 coverage <50%
A decision on the interval before the next SIA should be made on a case by case basis after detailed review of country data.

Follow-up SIAs represent a unique opportunity to reach preschool age children outside the routine health delivery system with measles vaccine as well as other child survival interventions. For this reason, follow-up SIAs should target all children ages 9 months to 59 months regardless of the interval since the last SIA.

Because inflated coverage numbers may lead to selection of an interval that is longer than that required to prevent outbreaks, WGM recommended that the most accurate estimates of routine coverage and campaign coverage (survey results if these are available) be used to determine the interval. If such estimates are not available countries may use the available administrative coverage estimates. In situations where routine coverage is rapidly changing, an average of the coverage in the first 2 years after the SIA should be used to calculate the interval.

With respect to splitting mass campaigns, catch-up SIAs should only be split or implemented in a rolling fashion if it is logistically not feasible to conduct a single nationwide campaign. If it is necessary to split an SIA, each phase should cover a large geographically contiguous area to minimize the risk of reintroduction of measles immediately following the campaign. In large countries (e.g., India) a statewide campaign can be considered equivalent to a nationwide campaign.

In the case where the catch-up SIA was split, the follow-up SIA should not be split (assuming this is logistically possible) and be conducted using the date of the earliest catch-up phase as the starting point for calculating the interval before the next SIA.

If outbreaks occur in the inter-campaign interval they should be investigated and responded to according to existing WHO guidelines. These outbreaks tend to be focal and of short duration involving particular high risk groups and/or areas. For this reason the response should be targeted to these settings and be done as soon as possible after identification of the outbreak. As a general rule the WGM recommended that outbreaks occurring before a scheduled SIA should not result in bringing forward the next scheduled SIA. However, if transmission is geographically widespread (definition: involving more than one province) and sustained (definition: lasting longer than 3 months) consideration may be given to advancing the date of the next national SIA.

As districts that experience outbreaks have often been identified as low performing areas in the preceding SIA, targeted efforts to strengthen service delivery (i.e., RED approach) should be implemented in these districts immediately after completion of the initial SIA. This will prevent outbreaks in these districts during the inter-campaign period.

If follow-up SIAs are delayed because of resource shortfalls or inability to achieve integration of other child survival components, these situations need to be dealt with on a case-by case basis keeping in mind that measles vaccination is usually the priority intervention.