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EXPANDED PROGRAMME ON IMMUNIZATION

Measles Control in the 1990s:

Introduction of High Titre Measles Vaccines

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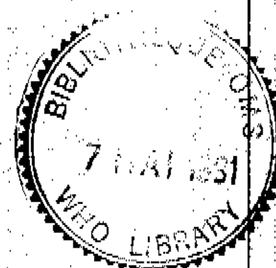
A Joint WHO/UNICEF Statement



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Appendix 1: Guidelines for developing a country plan for introduction of EZ-6 vaccine at 6 months

Appendix 2: Form for country request for EZ-6 vaccine

DEFINITIONS:

In this paper "**EZ-6**" is used to represent Edmonston Zagreb vaccine with a minimum potency of 4.7 log_{10} or similar vaccines approved for routine use at 6 months of age.

"**ST**" refers to standard titre vaccines currently being used at 9 months of age.

1. INTRODUCTION

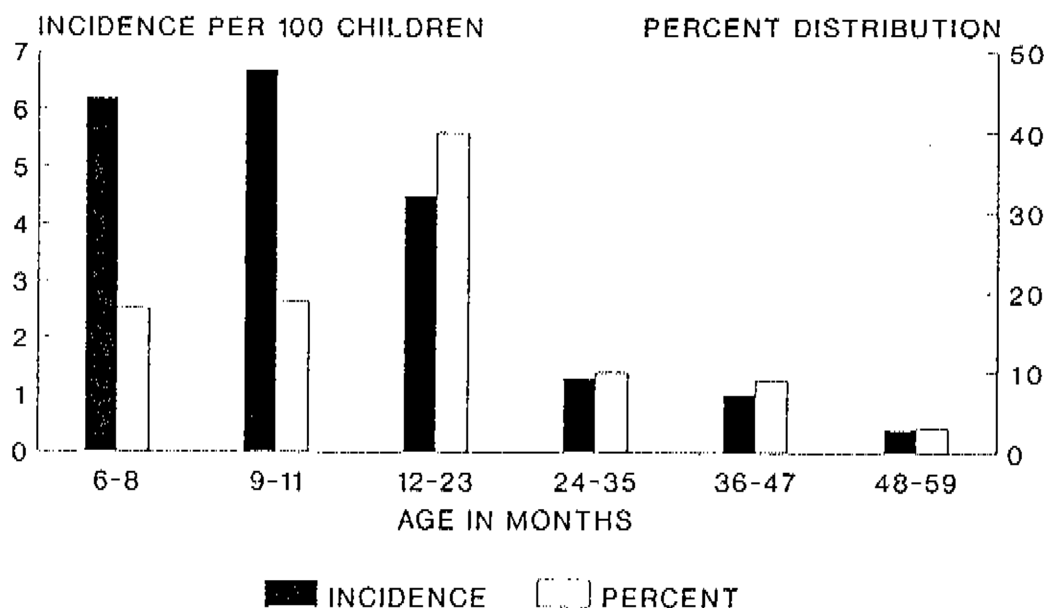
Measles is a major cause of infant and child mortality in the developing world resulting in an estimated 1.6 million deaths annually (Aaby 1989). Virtually all children surviving to the age of measles infection will suffer from measles and 1-5 % will die of measles and/or measles associated complications.

The introduction of measles vaccine as a Primary Health Care component has been effective in reducing measles morbidity and mortality in both the developing and the developed world. Data from Bangladesh (Clemens, Koenig), Haiti (Halsey) and Senegal (Garenne) document the effectiveness of measles vaccine not only in decreasing measles specific morbidity and mortality but also in decreasing total infant and child mortality.

Among developing world populations, attenuated measles vaccines strains at the standard titre of 1000 TCID50, ST, administered at 9 months of age are effective in preventing 75-85 percent of measles cases. High coverage with this vaccine has achieved effective measles control, especially among low and moderate density populations. However in densely populated areas, especially in African cities, significant numbers of measles cases continue to occur in children under nine months of age. Figure 1 summarizes age specific incidence data from Kinshasa, Zaire, a city which has obtained a 50% level of measles vaccine coverage, (Taylor). In this city 37% of cases still occur in the first year of life.

As measles case fatality rates are highest in the first year of life, development of a measles vaccine effective at 6 months of age or earlier has been identified as a high priority for the global immunization programme (WHO/EPI/GEN/90.2).

Figure 1. Measles age specific incidence and age distribution. Community survey, Kinshasa, Zaire 1983*



*TAYLOR ET AL, AM J EPI 1988,127:788-794

Trials with high titer Edmonston Zagreb measles vaccine have proven it to be as effective in providing serological protection when administered at 6 months of age as the ST vaccine administered at 9 months of age (WHO/EPI/GEN/90.3). In October 1989, the Global Advisory Group of the Expanded Programme on Immunization recommended that "high titre Edmonston-Zagreb (E-Z) measles vaccine be administered at 6 months of age, or as soon as possible thereafter, in countries in which measles before the age of 9 months is a significant cause of death." (Wkly Epidem Rec). A year later, the Global Advisory Group recommended the minimum titer for use at six months of age should be log $10^{4.7}$ infectious units per dose.

Based on the recognition that infant measles mortality is highest in epidemiological situations such as large urban agglomerates, initial allocations of EZ-6 vaccine are being targeted to such places, especially in Africa where infant mortality from measles is well documented.

Table 1 lists the estimated quantity of measles vaccine required to meet the global demand on UNICEF supplies. Africa alone was estimated to require over 60 million doses. The actual request from countries was nearly 15 % less than this. Additionally, manufacturers experienced production difficulties, making it difficult to meet targets. An additional 2-3 million doses of vaccine per year have been provided through bilateral channels.

UNICEF made tender agreements with manufacturers to supply 30 million doses of EZ-6 vaccine in 1990 and 40 million doses in 1991. However, production, licensing, and approval have all proved problematic, resulting in almost no EZ-6 being available in 1990 to fulfill the UNICEF tender. Only one manufacturer was licensed to provide EZ-6 to UNICEF up to the end of 1990. Current estimates of the availability of EZ-6 for 1991 are for 30 million doses for global distribution. If more manufacturers are approved, which is presently uncertain, more could become available.

In summary, scientific evidence now exists to demonstrate the safety and efficacy of immunizing against measles at six months of age. Vaccine supply for use at this age is still limited and does not permit global introduction of this policy. Some form of priority allocation is therefore essential.

Table 1.

Estimated Global Measles Vaccine Supply
data UNICEF Oct 1990

Region	
West and Central Africa	23.5
East and South Africa	23.8
Middle East and North Africa	15.5
Asia	23.8
Central and South America	10.5
GLOBAL	97.0

units millions of doses

2. ISSUES

Because the need for EZ-6 measles vaccine will initially exceed the available supply, WHO and UNICEF are assessing options for HT vaccine distribution. This document summarizes relevant issues and presents options for vaccine allocation from four perspectives: epidemiology, operations, logistics, and research.

2.1 Epidemiology

Two populations are at highest risk of morbidity and mortality from measles at 6-11 months of age:

1) refugees, especially new arrivals to camps (Toole), and
2) residents and visitors to large cities.

High risk of infection in the first year of life occurs in high population density areas where patterns of social interaction facilitate close contact of infants. Markets, at which mothers carry their babies on their backs, have been identified as a probable setting for transmission of measles between young infants. Refugee camps, public transport and health facilities, both outpatient and inpatient, are other sites for disease transmission.

Tables 2 and 3 estimate cases and deaths prevented per million doses of measles vaccine distributed according to four different vaccination strategies:

1) Current ST at 9 months;
2) EZ-6 at 9 months;
3) EZ-6 at 6 months;, and
4) EZ-6 at 6 months in high risk urban areas.

The calculations in this table are using best estimates and make some assumptions:

1. Coverage in many parts of Africa for measles vaccine administered at nine months is around 50%. It is assumed that administration of a measles vaccine at 6 months would increase coverage (and decrease drop-out).

2. It is assumed that a child is susceptible if he/she has not had measles disease. This is irrespective of presence or absence of maternal antibodies which will decline to zero in most individuals by 9 months of age. Only about 5% of children have had measles disease by 6 months (ie 95% remain susceptible). The percent having contracted wild measles by 9 months of age varies from place to place, but is taken here as 10% (90% remaining susceptible).

3. Vaccine efficacy is assumed to be 80% for ST vaccine administered at 9 months, 90% for EZ-6 at 6 months, and 95% for EZ-6 at 9 months.

4. Number of measles cases prevented = 1 million x % susceptible x V.E.

5. Case fatality rates are generally considered to be higher at younger ages and in densely populated urban environments.

TABLE 2. Estimated measles morbidity and mortality using alternative immunization strategies calculated for cohort of 1 million children

Strategy	ST at 9 mo	EZ-6 at 9 mo	EZ-6 at 6 mo	EZ-6 at 6 mo urban
Total cohort of children	1 million	1 million	1 million	1 million
Coverage[1]	50%	50%	60%	60%
Number immunized	500 000	500 000	600 000	600 000
Susceptible [2]	90%	90%	95%	95%
Number susceptible [2] among those immunized	450 000	450 000	570 000	570 000
Estimated vaccine efficacy[3]	80%	95%	90%	90%
Number of measles cases prevented by immunization[4]	360 000	427 500	513 000	513 000
Case fatality rate[5]	2%	2%	3%	4%
Number of measles deaths prevented	7 200	8 550	15 390	20 520

Table 3.
Additional measles cases and deaths prevented by immunization with EZ-6 measles vaccine at different ages and locations
(compared with immunizing with ST measles vaccine at 9 months of age)
calculated for cohort of 1 million children

Strategy	ST at 9 mo	EZ-6 at 9 mo	EZ-6 at 6 mo	EZ-6 at 6 mo urban
Number of measles cases prevented*	360 000	427 000	513 000	513 000
Number of measles deaths prevented*	7 200	8 550	15 390	20 520
Additional cases prevented (compared with ST at 9 mo)	-	67 500	153 000	153 000
Additional deaths prevented (compared with ST at 9 mo)	-	1 350	8 190	13 320

* figures derived in table 1.

Conclusion: From the epidemiological perspective of maximizing impact on measles mortality, large urban centers (meeting other criteria for vaccine allocation - see para 4 below) should receive priority in the allocation of EZ-6 vaccine.

2.2 Operations

Maximizing effective use of limited supplies of EZ-6 vaccine will be best achieved through preferential allocation of vaccine to programmes with established capability in vaccine logistics and delivery. Three criteria deserve consideration:

- An effective logistics system of vaccine storage and distribution with appropriate inventory control;

- A well functioning cold chain system of storage and distribution; and

- A vaccine delivery system which is effective in immunizing children in the first year of life.

Data on these three performance criteria are usually available from internal or external programme reviews. Programme effectiveness in providing measles vaccine in the first year of life can be estimated by comparing reported measles immunization under one with the total number of measles immunization. The percentage should be equal to or greater than 70%.

2.3 Logistics

Supplies of EZ-6 vaccine will not fully meet global needs for the next 2-4 years. If vaccines are to be provided to the areas of highest epidemiological risk, supplies will not be sufficient to meet the entire needs of those countries. In such a case, countries will require both EZ-6 and ST vaccines. Such a dual vaccine distribution system will require careful planning in supply (UNICEF), in-country storage and distribution, and use. Logistically easier options of meeting the entire vaccine needs of several smaller countries would have less impact on mortality, however.

2.4 Research

Research studies have documented the serological and clinical efficacy of the EZ-6 vaccine. Implementation studies are being initiated to resolve operational issues and to measure effectiveness of the change to EZ-6 vaccine and in reducing the age of immunization from 9 to 6 months. In Kinshasa, Zaire, for instance, EZ-6 vaccine is being introduced with a target of reducing measles incidence by 50% by 1992. More implementation studies are still needed in at least three areas:

- Testing of alternative vaccines for use at six months or earlier.

- Assessing long term protective efficacy of vaccines used at six months.

- Country-wide introduction of vaccine at six months of age.

3. PRIORITIES FOR ALLOCATING EZ-6 VACCINE

While EZ-6 vaccine can be safely introduced and used in the current immunization schedule at 9 months, a change in the age of immunization from 9 to 6 months need to be contingent on the long term availability of this vaccine. A reversion to ST vaccine after a change in the age of immunization from 9 to 6 months risks increased vaccine failures and a loss of programme credibility.

Recognizing that the amount of EZ-6 vaccine available in 1991 is not yet established, the issue was discussed at the WHO/EPI Research and Development Group Meeting of 15-16 March 1990 in Geneva. The following list of priorities for vaccine allocation were recommended:

1. In emergency situations in camps where **refugees** are at high risk of measles mortality in the first year of life.

2. In operational **studies** where an EZ-6 implementation trial has already been initiated, such as in Kinshasa, Zaire,

3. In other **research** projects recommended by the EPI R and D group.

4. In **urban areas** with populations greater than 1 million, which meet the criteria listed in 4.0 below. Allocation of vaccine to large cities would be contingent upon identification of a distinct programme and geographic area for vaccine use and a country vaccine utilization plan to ensure the appropriate use of EZ-6 and ST vaccines.

5. In **any country** demanding the vaccine.

Table 4.
Estimates and projected populations for the world's largest 45 urban agglomerates, ranked by 1985 population.

Based on data presented in "The Prospects of World Urbanization." Revised as of 1984-85, Population Studies, No. 101, St/ESA/SER/101, New York, 1987.

City	*Estimated population by the year 2000 in millions**	*City*	*Estimated population by the year 2000 in millions**
Tokyo	20.22	Chicago	7.03
Mexico City	25.82	Karachi	12.00
Sao Paulo	23.97	Bangkok	10.71
New York	15.78	Lima / Callo	9.14
Shanghai	14.30	Madras	8.15
Calcutta	16.53	Hong Kong	6.37
Buenos Aires	13.18	Leningrad	5.93
Rio de Janeiro	13.26	Dacca	11.16
London	10.51	Madrid	5.36
Seoul	13.77	Bogota	6.53
Greater Bombay	16.00	Baghdad	7.42
Los Angeles	10.99	Philadelphia	4.36
Osaka / Kobe	10.49	Santiago	5.26
Beijing	11.17	Naples	4.30
Moscow	10.40	Pusan	6.20
Paris	8.72	Shenyang	5.35
Jakarta	13.25	Bangalore	7.96
Tianjin	9.70	Caracas	5.03
Cairo / Giza	11.13	Lahore	6.16
Teheran	13.58	Lagos	8.34
Delhi	13.24	Belo Horizonte	5.11
Milan	8.15	Ahmedabad	5.28
Manila / Quezon	11.07		

* These data should be considered only as projected estimates. It is often difficult to determine precise numbers in cities with large proportions either migrant or living in shanty towns.

4. CRITERIA FOR ALLOCATING EZ-6 VACCINE TO COUNTRIES

The following criteria will be used by WHO and UNICEF in prioritizing the allocation of available supplies of EZ-6 vaccine:

1. 70% or more measles coverage in area(s) that EZ-6 vaccine is to be introduced.

2. Greater than 15% of measles cases in children under 9 months of age.

3. Appropriate systems of vaccine storage and distribution as verified by programme reviews or on-site WHO or UNICEF staff.

4. National policy which emphasizes measles immunization in the first year of life (->70% of measles immunizations administered to infants).

5. Functioning system of surveillance which is capable of monitoring trends in measles incidence and age distribution of cases.

6. Receipt of a country request for EZ-6 vaccine accompanied by specific plans for policy formulation, training, logistics, and evaluation. Appendix I outlines issues in developing a national plan for introducing EZ-6 vaccine. Appendix II provides a format for country request for EZ-6 vaccine.

5. METHOD OF APPLICATION BY COUNTRIES TO UNICEF FOR EZ-6

Requests should be submitted to UNICEF at country level who will pass this on to the UNICEF Copenhagen Office. It would be appreciated if country applications could also be copied to the WHO Country Representative, WHO Regional Office and WHO/EPI Geneva.

Quarterly, UNICEF (NY and Copenhagen) and WHO Geneva will review vaccine availability and make allocations to countries based on the above criteria.

6. REFERENCES

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APPENDIX 1

GUIDELINES FOR DEVELOPING A COUNTRY PLAN FOR INTRODUCTION OF EZ-6 VACCINE

1. Policy Development

1. Appoint an individual as responsible for assessment of the current situation and to develop a plan for introduction of EZ-6 vaccine.

2. Review available data from surveillance system, outbreak investigations, and published data pertaining to current measles epidemiology (age distribution of cases and age specific measles incidence).

3. Assess adequacy of data; if data are not sufficient, design a protocol for rapid assessment (outpatient register reviews) and collect data.

4. Utilizing a national technical committee and/or available professional experts, review available data and assess need for a change in vaccine policy.

5. Adopt policy change if indicated.

2. Training and Supervision

1. Identify target audiences needing information:
MOH officials, professional opinion makers (pediatricians, nurses), state/regional/provincial authorities, district/sector health officers, health facility staffs, communities and mothers.

2. For each target group, identify information needed, optimum method of presentation and resource requirements. Assess availability of resources optimizing the use of scheduled contacts.

3. Develop a training plan

4. Develop a supervision plan to support correct use of vaccine

3. Logistics

Introduction of EZ-6 vaccine will require an organized plan of phase over from ST to EZ-6 vaccine. Two options will need to be considered at the country level:

a. Introduce EZ-6 vaccine using current 9 month vaccine schedule and delay shift in age of immunization to 6 months until all ST strain vaccine has been used, or

b. Identify high risk areas for priority allocation of EZ-6 vaccine and immediately implement immunization at 6 months in those areas as soon as EZ-6 vaccine is available.

4. Monitoring and Evaluation

a. Assess implications of the policy change for recording and reporting

Road-to-health card
Monthly report of EPI activities
Coverage (estimates/surveys)
Annual report

b. Determine capacity of surveillance system to monitor:
Trends in disease incidence
Age distribution of case
Age specific incidence rates
Vaccine efficacy

c. Upgrade surveillance as needed to meet the above needs.

APPENDIX 2.
COUNTRY REQUEST FOR EZ-6 VACCINE

1. Country ______________

2. EPI target population age in months ______ to ________

3. Number of children surviving to one year_____________

4. Last year immunization data available 19____

5. Number of measles immunizations given to <1 _________________

6. Estimated measles vaccine coverage of <1 year olds (#5/#3x100)_______ %

7. Total number of measles immunizations ________________

8. % Measles immunizations to <1 year olds (#5/#7x100) _______ %

9. Current measles coverage 12-23 months by survey _______ %

10. Number of measles cases on which age is available? _______

11. % of above cases 6-8 months ____ %,
    % of above cases 9-11 months ____ %

12. Target areas for introduction of EZ-6

    Total Country _____ or__________________________

13. Target age for EZ-6 from age _____ to _______

14. Number in target population (annual) ___________

15. Quantity EZ-6 needed 1991 _______ , in 1992__________.

15. Date Ministry of Health Approval for use of EZ-6 at 6 months.

    ____

Attach plan (maximum 2 pages) on how country plans to introduce EZ-6 vaccine.