CENTERS FOR DISEASE CONTROL

EIS Summer Course: Measles

(Revised: June 1992)

A Measles Outbreak in a Highly Vaccinated Population: Health Sector Muyinga, Burundi, 1988-1989

Objectives:

After completing this case study, the student should be able to:

- 1. Discuss methods for evaluating vaccination coverage, including their advantages and disadvantages.
- 2. Interpret surveillance data to assess the impact of vaccination programs.
- 3. Describe methods to estimate vaccine efficacy and discuss their most common biases.
- 4. Recognize the advantages and limitations of selecting specific ages as the recommended target ages for administering vaccines.
- 5. Describe the role of susceptibles and immunes in epidemic cycles, and the changes induced by a vaccination program.

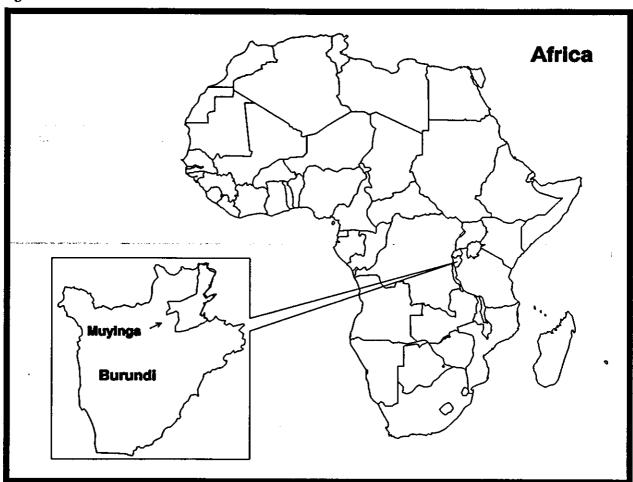
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PART I

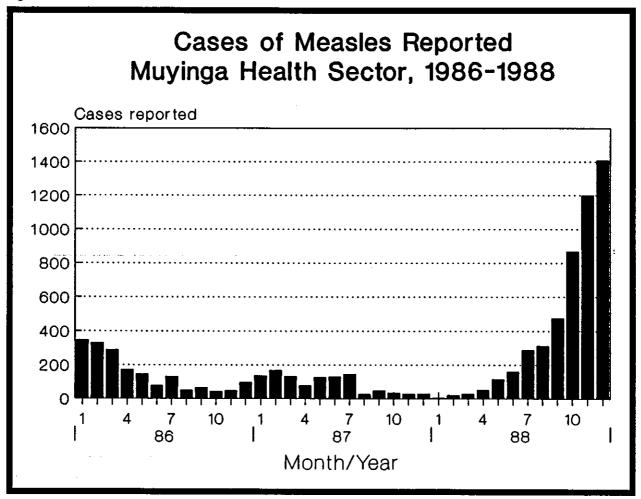
Figure 1



Burundi is a small densely populated nation located in east-central Africa, divided into 24 health sectors. Vaccination against measles, targeted at children 9-23 months of age, was introduced in 1981 in Burundi as part of the World Health Organization's (WHO) Expanded Programme on Immunization (EPI). Between 1985 and 1988, extensive resources (e.g., vaccines, syringes, refrigerators, transport, fuel) were invested in the Burundi EPI with the assistance of UNICEF and other donors as part of an initiative to improve child survival.

In late 1988, the estimated vaccine coverage in Burundi was at its historical high. Surprisingly, a measles epidemic was reported from Health Sector Muyinga, a sector located in northeast Burundi that had previously received excellent EPI program reviews (Figure 2).

Figure 2



QUESTION 1: In view of this epidemic, questions were raised as to whether the extensive resources spent on EPI had been worthwhile. What studies would you do first?

One of the first tasks of EPI staff was to verify information available on measles vaccination coverage. Vaccination coverage can be estimated by the "administrative method," based on routine reports of doses of vaccine administered, or by coverage surveys.

Administrative Method: the measles vaccination coverage of children 12-23 months of age can be calculated as the number of doses received by children 12-23 months old, divided by the number of children 12-23 months old. The number of children 12-23 months old is estimated by the number of "surviving infants," which is the number of children born alive the previous year, minus the number of infants who died before the age of 1 year:

Surviving Infants (SI) = Live Births (LB) - Infant Deaths (ID)

OUESTION 2: Assuming a crude birth rate of 4.8% and an infant mortality rate of 10.5%, calculate the number of surviving infants born in 1987 in Burundi, and in 1983 and 1987 in Health Sector Muyinga (1983 and 1985 figures for Burundi are given as examples).

Table 1.	Surviving	infants	in	Burundi
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Birth	Population	Live births (pop x 4.8%)	Infant deaths (LB x 10.5%)	Surviving infants (LB - ID)
1983	4,400,000	211,200	22,176	189,024
1985	4,700,000	225,600	23,688	201,912
1987	4,900,000			

Table 2. Surviving infants in Health Sector Muyinga

Birth	Population	Live births (pop x 4.8%)	Infant deaths (LB x 10.5%)	Surviving infants (LB - ID)
1983	287,000			
1987	322,000			

All health centers submit a Monthly Vaccination Report on doses of vaccines administered to each of two age groups: 0-11 months and 12-23 months. The target age for measles vaccination in the Burundi EPI is 9-23 months, and all doses of measles vaccine administered to children 0-11 months on the Monthly Vaccination Report are assumed to have been given at 9-11 months. Strictly speaking, the number of doses received by children before the age of 24 months is the sum of the number of doses administered to children ages 12-23 months during year (Y) plus the number of doses administered to children ages 9-11 months during year (Y-1). Thus, the estimated coverage for children who reached age 24 months during year Y should be written as follows:

ESTIMATED COVERAGE = [Doses 12-23 mo. year (Y)] + [Doses 9-11 mo. year (Y-1)]

Surviving Infants Born in year (Y-1)

<u>QUESTION 3</u>: Estimate the measles vaccination coverage in Burundi in 1988, and in Health Sector Muyinga in 1984 and 1988.

Table 3. Measles vaccination coverage, Burundi

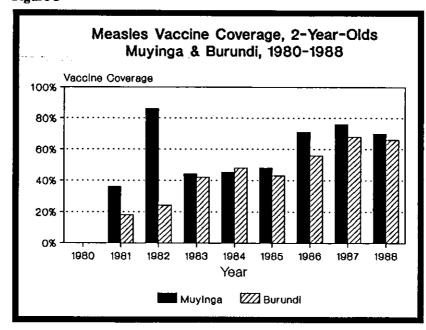
Year	Doses administered 12-23 mo (Y) + 9-11 mo (Y-1)	Surviving infants born year (Y-1)	Coverage
1984	90,020	189,024	48%
1986	110,436	201,912	55 %
1988	138,140	210,504	

Table 4. Measles vaccination coverage, Health Sector Muyinga

Year	Doses administered 12-23 mo (Y) + 9-11 mo (Y-1)	Surviving infants born year (Y-1)	Coverage
1984	5,430	12,330	
1988	######################################	13,833	

Figure 3 shows the measles vaccination coverage estimated by the "Administrative Method" for Muyinga and Burundi for 1980-1988. Note that Muyinga introduced measles vaccination by a mass campaign in 1981, targeting children 9-23 months of age, which resulted in a peak in coverage in 2-year-olds in 1982. Since 1987, coverage in Muyinga has generally exceeded the national average. Note also that coverage levels have improved by at least 20% since "acceleration" of EPI in 1986.

Figure 3



Coverage Surveys: A simple random-sample survey is rarely feasible, since it requires a complete enumeration of all children in the target age group. "Convenience Sample" surveys rely on non-random samples, such as children attending certain schools or residing in a selected area. The WHO-EPI 2-Stage, 30-Cluster Survey technique was developed to obtain representative samples when a complete enumeration of all children is not available. The first-stage sampling involves the selection of 30 villages or quarters, each village having a probability of being selected proportionate to its size. The second stage is the random selection, in each selected village, of the first household to be visited. As many consecutive households as necessary will then be visited until seven children 12-23 months of age are found. The sample size of 30 x 7 children has been selected to permit an estimate within 10% of the true coverage.

Table 5 represents selected results from the coverage surveys done in Muyinga in 1984 and in Burundi in 1986, with comparable estimates based on the administrative method.

Table 5. Measles vaccination coverage, 12- to 23-month-olds

Location	Year	Coverage survey	Administrative method
Burundi	1986	57% (WHO-EPI 30 Cluster)	55%
Muyinga	1984	73% (Convenience Sample)	44%

OUESTION 4: Compare the coverage results obtained by the "Administrative Method" (from Tables 3-4) with the results from the coverage surveys. Discuss advantages and disadvantages of each method.

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PART II

The Burundi Monthly Epidemiologic Bulletin Report was initiated in 1980. An estimated 90% of all health facilities submit a monthly report of case counts and deaths for measles and 27 other illnesses. Figures 4 and 5 summarize the 1980-1988 measles incidence and mortality data available to the EPI office, as well as the chickenpox incidence reported via the same surveillance system.

Figure 4

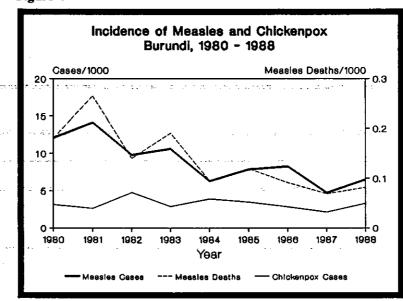
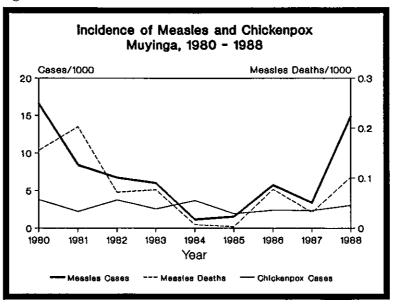
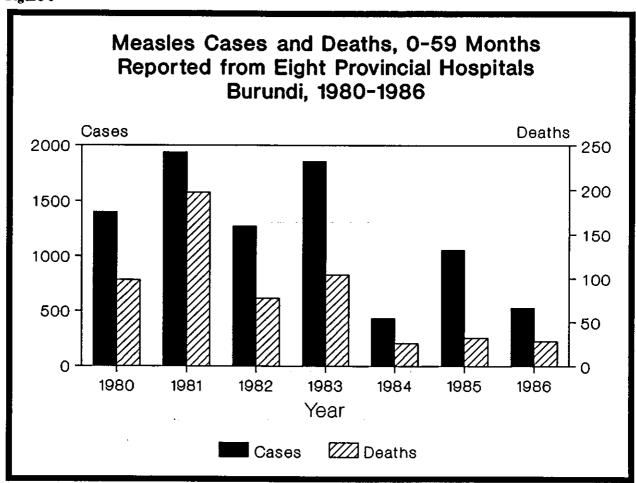


Figure 5



A recently completed study based on the registries of the eight major provincial hospitals provided additional data on persons admitted to hospitals for measles and deaths from measles, summarized in Figure 6.

Figure 6



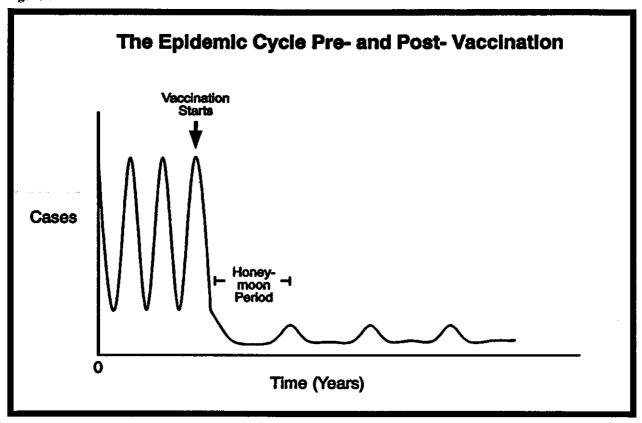
QUESTION 5: Describe and interpret the trends in measles morbidity and mortality in Burundi.

<u>QUESTION</u> 6: Use data on chickenpox incidence in Figures 4-5 to discuss the validity of the trends in measles incidence observed via routine surveillance.

OUESTION 7: What can you conclude about the impact of EPI on measles control in Burundi?

Figure 7 represents the epidemic cycle of measles in a rural region before and after the introduction of measles vaccination.

Figure 7



QUESTION 8: Why do certain communicable diseases such as measles have regular epidemic cycles?

<u>QUESTION 9</u>: In rural areas, the introduction of a vaccination program generally results in a lengthening of the period between measles epidemics (Figure 7). Can you explain why?

In Muyinga, records of measles cases by age group and vaccination status were available since 1985. Table 6 provides information on the age distribution of persons with measles in Muyinga.

Table 6. Measles Cases and their Percent Age Distribution, Muyinga, 1985-1988

Year	1985	1986	1987	1988
Measles Cases	468	1,791	1,084	4,867

0-11 months	15%	26%	31%	24%
12-23 months	55 %	32%	26 %	19%
24+ months	30%	42%	43 %	57%
Total	100%	100%	100%	100%

QUESTION 10: Describe and interpret the changes in the age distribution of measles cases in Muyinga.

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PART III

During the 1988 outbreak, both parents and health-care workers noted that many of the measles cases occurred among children who had documentation of measles vaccination. This suspicion was confirmed when the surveillance data on vaccination status of persons with measles from Muyinga (available since 1985) were reviewed.

Table 7. Vaccination status of measles cases, Muyinga

Year	Number of measles cases	Proportion of cases vaccinated	Vaccine coverage in population
1984	338	N/A	45%
1985	468	7%	48%
1986	1,791	14%	71%
1987	1,084	30%	76%
1988	4,867	28%	70%

QUESTION 11: Can you conclude from these data that there is a problem with vaccine efficacy?

Table 8 allows you to calculate the Percent Cases Vaccinated (PCV), for three different values of vaccine coverage. Assume a population of 100, a vaccine efficacy of 90%, and a disease which affects all susceptibles (all unvaccinated become ill). Calculations for PPV = 20% are given as example.

Table 8. Hypothetical populations with vaccine coverage of 20%, 60%, and 100%

a. Total population	100	100	100
b. Vaccine efficacy (VE)	90%	90%	90%
c. Percent population vaccinated (PPV)	20%	60%	100%
d. Number vaccinated (axc)	20		
e. Number unvaccinated (a-d)	80		
f. Number protected (dxb)	. 18		
g. Number vaccinated but ill (d-f)	2		
h. Total number ill (e+g)	82		
i. Percent cases vaccinated (PCV) (g/h)	2.4%		

QUESTION 12: Complete Table 8. What can you conclude about the relationship between coverage and number of cases vaccinated?

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The ability of a vaccine to prevent disease depends on its potency and proper administration to an individual capable of responding. The success of vaccination performed under field conditions may be assessed by measuring protection against clinical disease. It can be very useful, particularly when doubt is cast on the efficacy of the vaccine because of the occurrence of disease among vaccinated persons.

Vaccine efficacy is measured by calculating the incidence (attack rate) of disease among vaccinated and unvaccinated persons and determining the percentage reduction in incidence of disease among vaccinated persons relative to unvaccinated persons. The greater the percentage reduction of illness in the vaccinated group, the greater the vaccine efficacy. The basic formula is written as:

$$VE = (ARU - ARV) / ARU = 1 - (ARV / ARU) = (1 - RR)$$

(Where VE = vaccine efficacy; ARU = attack rate for unvaccinated; ARV = attack rate for vaccinated; and RR = relative risk)

To examine vaccine efficacy, in January 1989, a door-to-door census was conducted of all households with children 0-5 years old in the five districts in Muyinga hardest hit by the epidemic. Trained interviewers recorded the date of birth, date of measles vaccination, measles disease status (according to mother's assessment), and survival for each child. Measles vaccination was accepted only if documented by a vaccination card. A separate questionnaire on symptoms was completed for each person with measles. The results of this census are shown below (Tables 9A-9D):

<u>OUESTION 13:</u> Using the equation provided above, calculate the vaccine efficacy for Tables 9B-9D (calculations for Table 9A are given as an example). Discuss the reasons for the differing results obtained.

Table 9A. All children in census (measles cases as reported by mother; children without vaccination card counted as unvaccinated)

	Measles	No measles	Total
Vaccinated	109	843	952
Unvaccinated	182	607	789
Total	291	1,450	1,741

$$ARU = 182/789 = 23.1\%$$
 $ARV = 109/952 = 11.4\%$

$$VE = ([182/789] - [109/952]) / [182/789] = 50.4\%$$

Table 9B. Unvaccinated children restricted to those with vaccination cards (on which there is no record of measles vaccination).

	Measles	No measles	Total
Vaccinated	109	843	952
Unvaccinated	121	309	430
Total	230	1,152	1,382

Table 9C. Criteria in 9B and measles cases restricted to those with symptoms meeting the case definition of fever, rash and cough, or runny nose or red eyes.

	Measles	No measles	Total	
Vaccinated	49	843	892	
Unvaccinated	59	309	368	
Total	108	1,152	1,260	

Table 9D. Criteria in 9B and 9C and analysis restricted to children ≥ 9 months of age

	Measles	No measles	Total
Vaccinated	48	840	888
Unvaccinated	44	116	160
Total	92	956	1,048

 The attached nomogram (Figure 8, next page) provides a quick method, known as the "screening method," to estimate vaccine efficacy. Each curve represents, for a specific value of vaccine efficacy, the relation between vaccine coverage (or PPV, for percentage of population vaccinated) and PCV, or percentage of cases vaccinated. As an example, if vaccine coverage is estimated as 60%, and if 30% of the persons with measles have been vaccinated, the nomogram indicates a vaccine efficacy of approximately 70%.

QUESTION 14a: Using the nomogram and the information on 12- to 23-month-olds in Muyinga provided in Table 10, estimate vaccine efficacy by the "screening method" (estimate of Vaccine Efficacy for 1985 is given as example).

Table 10. Vaccine coverage (PPV) and proportion of cases vaccinated (PCV), 12- to 23-month-olds, Muyinga

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Year	PPV	PCV	VE (from nomogram)
1985	48%	6%	93%
1986	71%	17%	
1987	76%	41%	
1988	70%	31%	

QUESTION 14b : Compare these	estimates	with the vac	cine efficacy	obtained	in Question	13.
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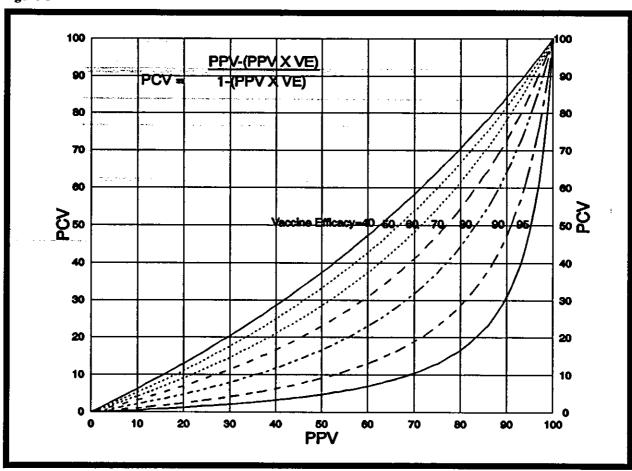
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Nomogram: Percentage of cases vaccinated (PCV) per percentage of population vaccinated (PPV), for seven values of vaccine efficacy (VE).

$$PCV = \frac{PPV - (PPV \times VE)}{1-(PPV \times VE)}$$

Each curve corresponds to one value of vaccine efficacy (VE); from left to right, VE = 40%, 50%, 60%, 70%, 80%, 90%, and 95%.

Figure 8



Source: Field Evaluation of Vaccine Efficacy, W.A. Orenstein et al., Bull WHO 1985;63(6):1055-68.

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PART IV

The target age group for measles vaccination in the Burundi EPI has remained unchanged at 9-23 months of age since its inception. Unvaccinated children outside this age group have been turned away from health centers without receiving measles vaccine. From Table 6, it is clear that close to two-thirds of the cases during the 1988 outbreak were among children outside the target age, a situation extremely difficult to explain to the mothers in Muyinga. A series of special studies were conducted to examine age-specific issues. From the census, the following data were also obtained on age-specific morbidity:

Table 11. Measles attack rate by age group, Muyinga census

Age group	Census	Measles cases	Attack rate	% of total
0-5 months	206	18	9%	6%
6-8 months	142	45	32%	15%
9-23 months	522	124	24%	42%
24-59 months	900	108	12%	37%
TOTAL	1,770	295	17%	100%

Because measles depresses the immune system and nutritional status of the child for several months after disease, members of households in the original census were reinterviewed 10 months after the peak of the outbreak to examine age-specific cumulative mortality:

Table 12. Age-specific mortality by measles-disease status

	III	with measles	S		No measles				
Age (months)	Total	Died	(%)	Total	Died	(%)	Excess mortality		
0-5	19	3	15.8	200	9	4.5	11.3%		
6-8	45	2	4.4	119	3	2.5	1.9%		
9-23	128	9	7.0	389	17	4.4	2.7%		
24-59	124	3	2.4	844	28	3.3	-0.9%		
Total	316	17	5.4	1,552	57	3.3	1.7%		

A separate census was conducted at Cumba grade school in Muyinga, to examine the impact of the outbreak on children in this age group and the transmission to their household contacts:

Table 13. Measles cases, Cumba Primary School, 1988

Grade	Enrollment	Measles cases	Attack rate	Primary cases*	% of Cases	
1	67	9	13%	9	100%	
2	59	2	3%	2	100%	
3	60	9	15%	6	67%	
4	69	7	10%	7	100%	
5	44	1	2%	1	100%	
Total	299	28	9%	25	89 %	

^{*} Primary cases (in a household) = Measles cases in children who were the first person with measles in their households. These 25 primary cases were followed by a total of 31 secondary household cases, 28 (90%) of which were among younger siblings.

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OUESTION 16: Discuss the main reasons for the 1988 measles outbreak in Muyinga. Should similar outbreaks be expected in other regions or countries?

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OUESTION 17: Discuss means of preventing similar outbreaks and of minimizing their impact, especially with respect to the morale of the staff and the credibility of the program.

QUESTION 18: Can measles outbreaks in locations with good vaccination programs be assumed to be due to the "post-honeymoon period" phenomenon?

- NOTES -

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PART V - CONCLUSIONS

The appropriate target age for vaccination is a tradeoff between age-specific morbidity, mortality, role in measles transmission, and available resources. Measles incidence is lowest for children 0- to 5-months-old due to residual maternal antibody. Incidence then increases rapidly for older children though their mortality is lower. School-age children appear to be important sources of infection to younger siblings at higher risk, however.

In Burundi, the decision was made that to prevent future buildup of susceptibles, the primary focus of the program still needs to be immunizing as large a proportion of each birth cohort as possible, as soon as possible after they become eligible for vaccination (also called age-appropriate immunization).

When resources are available, unvaccinated children older than 23 months of age will be vaccinated when they come into contact with the health care system. The age of measles vaccination will also be lowered to 6 months of age when a new more potent measles vaccine (Edmonston-Zagreb) becomes available. This will further reduce the gap of susceptibility between maternal and vaccine-derived immunity.

Outbreaks such as the one in Muyinga have been named "post-honeymoon-period outbreaks." Even with a "successful" immunization program like the Muyinga EPI, susceptibles will still accumulate as long as there is less than 100% vaccine coverage and the vaccine used is less than 100% efficacious.

A rapid improvement in vaccine coverage results in a honeymoon period of low incidence during the transition to a new equilibrium with a lower incidence and a longer interepidemic period.

But for highly contagious diseases such as measles, even with excellent vaccine coverage, another outbreak is just a question of time, as long as susceptibles are accumulating. In the United States, large measles outbreaks were experienced in 1989-1990 after ten years of very low incidence and vaccine coverage of primary school enterers of >95%.

Paradoxically, such "post-honeymoon-period" outbreaks tend to strike when one might least expect: a) when vaccine coverage has reached its historical highs, and b) when disease incidence has reached its historical lows. The timing of such type of outbreaks may lead to demoralization of EPI staff and loss of credibility in the EPI. This would be unfortunate because such outbreaks may be EXPECTED with a good understanding of measles epidemiology - and such outbreaks are likely in other EPIs!!

The key to preventing "post-honeymoon-period" outbreaks is to prevent accumulation of the two major sources of susceptibles: a) unvaccinated, and b) vaccine failures, which are of two types: 1) primary: those who fail to seroconvert initially, and 2) secondary: those who seroconvert, but whose immunity subsequently wanes.

Possible control strategies depend on cost-benefit analysis:

- a) reduce the unvaccinated population by age-appropriate vaccination of as much of each birth cohort as possible.
- b) vaccinate older unvaccinated susceptibles, including immigrants, using 1) health-care contacts, 2) special campaign, 3) school based programs.
- c) vaccinate vaccine failures via a routine second dose.

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EPI staff and health professionals need to be educated about this phenomenon to reduce demoralization. Media and other policy makers need to be educated to prevent unnecessary loss of program credibility. Focus should be on long-term incidence rather than acute outbreak. Communication should emphasize that high coverage has prevented large numbers of cases and deaths during the period of low incidence, and that higher overall coverage and reduction of pockets of low coverage, will still prevent larger numbers of cases and deaths, and prevent transmission to younger unvaccinated siblings. Even with coverage as high as in Muyinga, the majority of cases still occur in unvaccinated.

Social expectations may change during the honeymoon period such that when the post-honeymoon outbreak arrives, outbreaks are no longer "acceptable" and great political pressure is generated to "control" it. This may divert resources from important routine age-appropriate vaccination, however (leading to susceptibles for the next outbreak). Also, the outbreak may be over by the time resources are mobilized. Best action is still prevention as opposed to reaction.

Measles outbreaks in locations with good vaccination programs can not automatically be assumed to be due to the "post-honeymoon-period" phenomenon without further investigation. Outbreaks in locations with vaccination programs can result from accumulation of susceptibles from a) unvaccinated and b) vaccine failures. Some causes of primary vaccine failure may be preventable (e.g., poor cold chain, poor administration technique, administration before target age). An investigation is always needed to confirm that vaccine efficacy is within expected limits. Only then can the outbreak be attributed to the "post-honeymoon-period" phenomenon.

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A Measles Outbreak in a Highly Vaccinated Population: Health Sector Muyinga, Burundi, 1988-1989

PART II - OPTIONAL

The Burundi Monthly Epidemiologic Bulletin Report was initiated in 1980. An estimated 90% of all health facilities submit a monthly report of cases and deaths for measles and 27 other illnesses. Tables F-4 and F-5 summarize for Burundi and for Health Sector Muyinga the 1980-1988 estimated population, the measles cases and measles deaths counts available to the EPI office, as well as the chickenpox cases reported via the same surveillance system.

QUESTION 5a:

Using Tables F-4 and F-5, calculate measles incidence, measles mortality, and chickenpox incidence rates for Burundi and Muyinga, 1980-1988. Figures for 1980 are given as example.

Table F-4: Total Population, Measles and Chickenpox Cases and Measles Deaths, Burundi, 1980-1988.

Year	1980	1981	1982	1983	1984	1985	1986	1987	1988
Population x1000	4,100	4,200	4,300	4,400	4,500	4,700	4,800	4,900	5,100
Measles Cases	49,227	58,970	42,051	46,732	28,587	36,740	39,605	23,297	33,133
Measles Deaths	732	1,106	602	841	431	558	437	340	426
Chickenpox Cases	12,776	11,033	20,377	12,756	17,703	16,348	13,633	10,537	16,890
Measles Cases /1000	12.01								
Measles Deaths /1000	0.18								
Chickenpox Cases /1000	3.12								

Table F-5: Total Population, Measles and Chickenpox Cases and Measles Deaths, Muyinga, 1980-1988.

Year	1980	1981	1982	1983	1984	1985	1986	1987	1988
Population x1000	264	272	279	287	295	304	313	322	331
Measles Cases	4,384	2,287	1,880	1,723	338	468	1,791	1,084	4,867
Measles Deaths	41	55	20	22	2	1	24	10	34
Chickenpox Cases	1,007	599	1,044	736	1,079	578	750	751	1,006
Measles Cases /1000	16.61								
Measles Deaths /1000	0.16								

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Сь	ickenpox Cases /1000	3.81				
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QUESTION 5b:

Draw the corresponding graphs (Figures 4-5).

Figure 4

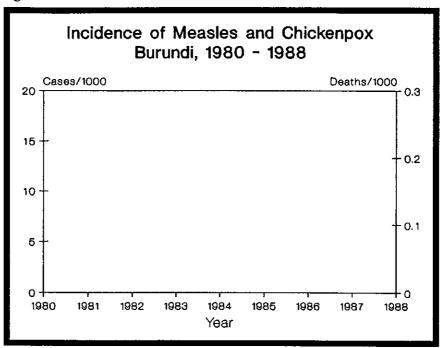
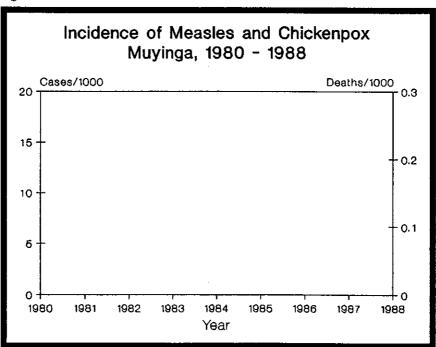


Figure 5



A recently completed study based on the registries of the eight major provincial hospitals provided additional data on measles cases admitted to hospitals and measles deaths, summarized in Table F-6.

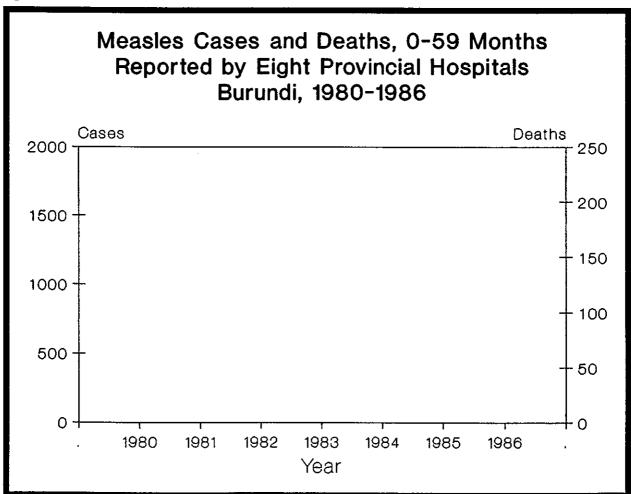
Table F-6: Measles Cases and Measles Deaths, 0-59 months, 8 Selected Hospitals, Burundi, 1980-1986.

Year:	1980	1981	1982	1983	1984	1985	1986
Measles Cases	1,400	1,936	1,272	1,852	435	1,054	530
Measles Deaths	98	197	77	104	26	32	28

QUESTION 5c:

Represent on a graph (Figure 6) the data on measles cases and measles deaths in hospitals presented in Table F-6.

Figure 6



QUESTION 5d:

Using Figures 4-6, describe and interpret the trends in measles morbidity and mortality in Burundi and Muyinga.

QUESTION 6:

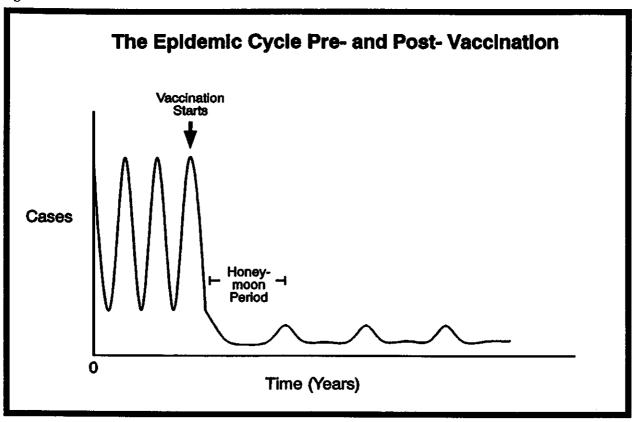
Use data on chickenpox incidence in Figures 4-5 to discuss the validity of the trends in measles incidence observed via routine surveillance.

QUESTION 7:

What can you conclude about the impact of EPI on measles control in Burundi?

Figure 7 represents the epidemic cycle of measles in a rural region before and after the introduction of measles vaccination.

Figure 7



<u>OUESTION</u> 8: Why do certain communicable diseases such as measles have regular epidemic cycles?

QUESTION 9: In rural areas, the introduction of a vaccination program generally results in a lengthening of the period between measles epidemics (Figure 7). Can you explain why?

In Muyinga, records of measles cases by age group and vaccination status were available since 1985. Table 6 provides information on the age distribution of persons with measles in Muyinga.

Table 6. Measles Cases and their Percent Age Distribution, Muyinga, 1985-1988

Year	1985	1986	1987	1988
Measles Cases	468	1,791	1,084	4,867

0-11 months	15%	26%	31%	24%
12-23 months	55%	32%	26%	19%
24+ months	30%	42%	43%	57%
Total	100%	100 %	100%	100%

OUESTION 10a:

Using data from Table 6, represent graphically the Percent Age Distribution of Measles Cases (Figure 9) and the Measles Cases by Age Group (Figure 10).

QUESTION 10b:

Using Figures 9-10, describe and interpret the changes in the age distribution of measles cases in Muyinga.

Figure 9

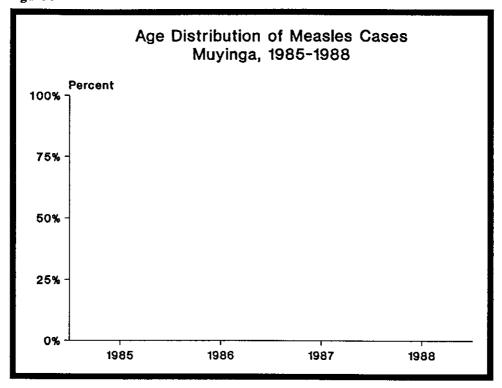
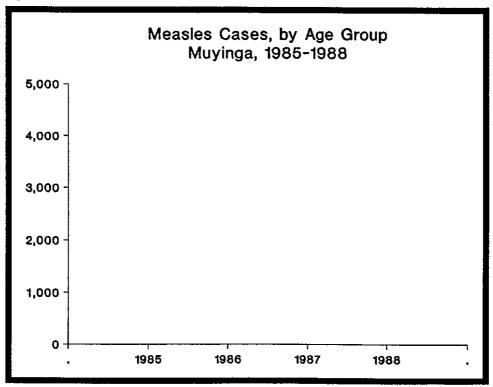


Figure 10



-- NOTES --