Centers for Disease Control and Prevention
Epidemiology Program Office
Case Studies in Applied Epidemiology
No. 911-102

A Measles Epidemic in a Highly Vaccinated Population ("Measles in Burundi")

Student's Guide

Learning Objectives

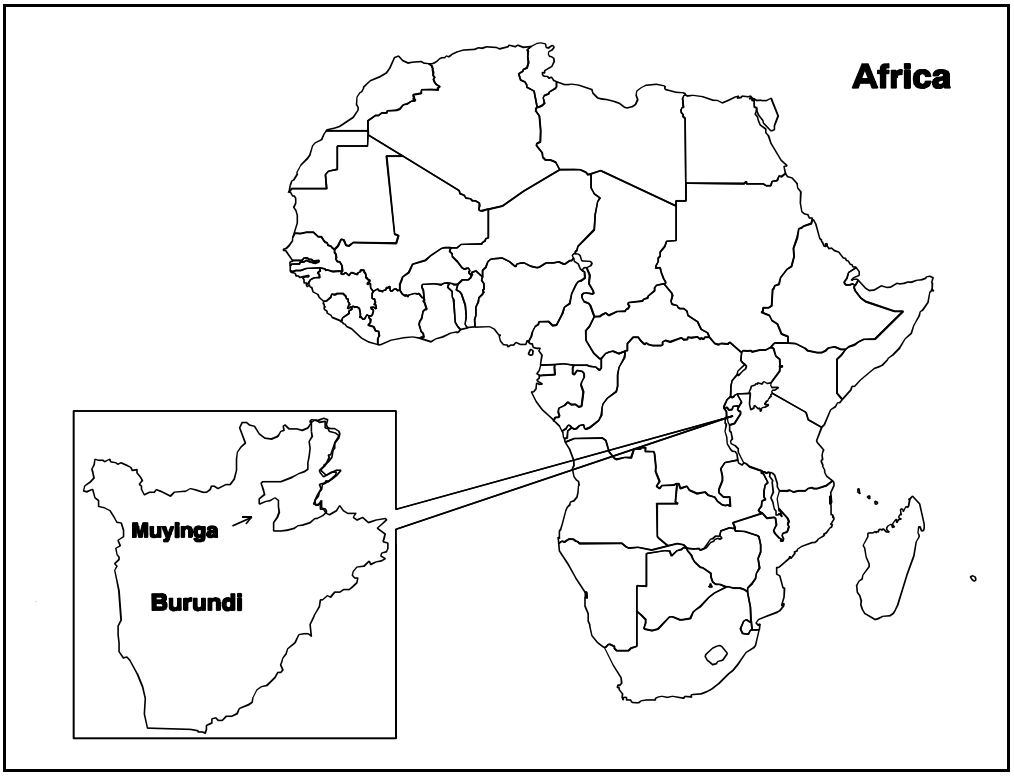
After completing this case study, the participant should be able to:

- Discuss methods for estimating vaccination coverage;
- Describe the difference between a convenience sample and a probability sample;
- Describe the sampling method used in WHO-EPI surveys; and
- Calculate and interpret vaccine efficacy, and describe the effect of varying the case definition on this measure.

This case study was developed by Robert Chen and Bernard Morniere in 1991. It was adapted for use in the EIS Summer Course by Robert Chen, Bernard Morniere and Richard Dicker.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

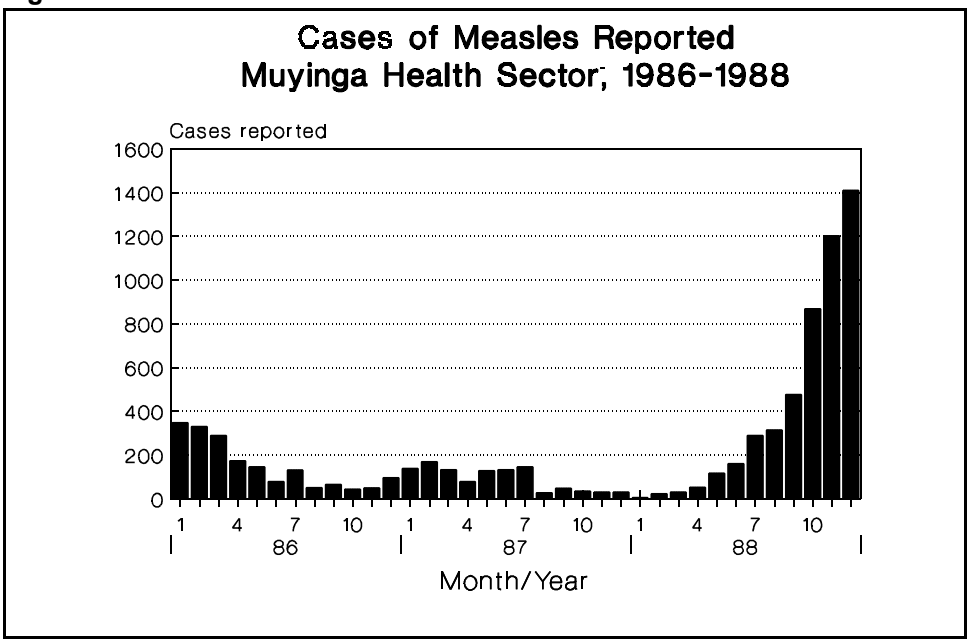
PART I - Vaccine Coverage



Burundi is a small densely populated nation located in east-central Africa. It is 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, as part of an initiative to improve child survival, UNICEF and other donors invested substantial resources, such as vaccines, syringes, refrigerators, transport, and fuel, in the Burundi EPI.

In late 1988, the estimated vaccine coverage in Burundi was at its historical high. At the same time, Health Sector Muyinga, a sector in northeast Burundi, reported a dramatic increase in the number of measles cases diagnosed (Figure 2). This increase surprised the EPI central staff, since the EPI program in Health Sector Muyinga was highly regarded.

Figure 2.



Question 1: In general, what factors can account for a sudden increase in the number of reported cases of a disease? Which of these factors are plausible in this setting?

The increase in reported cases evidently reflected a true epidemic of measles. In light of this epidemic, some officials began to question whether the vast resources spent on EPI had been a wise expenditure.

Question 2: What are possible explanations (hypotheses) for this epidemic? What information might you like to have to explore these hypotheses?

The first task taken on by the central EPI staff was to estimate measles vaccine coverage in Burundi at large and in Muyinga specifically.

Question 3: How might you estimate measles vaccine coverage?

One method for estimating vaccine coverage is the so-called "Administrative Method." This method relies on data which should be readily available to program managers. Basically, coverage is calculated as a proportion in which the numerator is the number of doses of vaccine administered to the target population, and the denominator is the estimated size of the target population. 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)

Question 4: Using the data in Table 1, 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). Assume a crude birth rate of 4.8% and an infant mortality rate of 10.5%.

Table 1. Estimated number of surviving infants in Burundi, 1983, 1985, and 1987.

Year	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. Estimated number of surviving infants in Health Sector Muyinga, 1983 and 1987.

Year	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:

$$\textbf{ESTIMATED COVERAGE} = \frac{[\text{Doses 12-23 mo. year (Y)}] + [\text{Doses 9-11 mo. year (Y-1)}]}{\text{Surviving Infants Born in year (Y-1)}}$$

Question 5: Using the data in Tables 3 and 4, estimate the measles vaccination coverage in Burundi in 1988, and in Health Sector Muyinga in 1984 and 1988.

Table 3. Estimated measles vaccination coverage using administrative method, Burundi, 1984–1988.

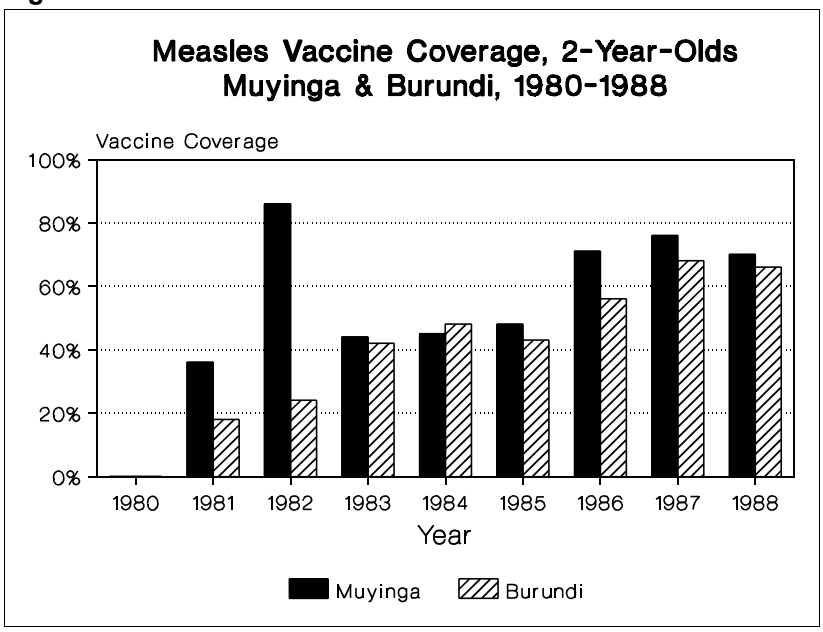
Year	Doses administered 12-23 mo (Y) + 9-11 mo (Y-1)	Surviving infants born year (Y-1)	Coverage
1984	90,020	189,024	48%
1986	110,436	201,912	55%
1988	138,140	210,504	_____

Table 4. Estimated measles vaccination coverage using administrative method, Muyinga, 1984 & 1988.

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	9,450	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 1981, 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



Question 6: What are the advantages and disadvantages of the "Administrative Method"?

A second way of estimating vaccine coverage is by conducting a field survey, and determining vaccination status for a sample of children. In 1984, vaccine coverage was estimated to be 73% in Muyinga based on a convenience sample.

Question 7: What is a convenience sample? What other types of sampling strategy might you propose for a vaccine coverage survey in this setting?

The method preferred by EPI is the WHO-EPI 2-step, 30-cluster survey technique. 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 are visited until seven children 12-23 months of age are found. The sample size of 30 x 7 children provides 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
Muyinga	1984	73% (Convenience Sample)	44%
Burundi	1986	57% (WHO-EPI 30 Cluster)	55%

Question 8: Compare the coverage results obtained by the "Administrative Method" (from Tables 3-4) with the results from the coverage surveys.

In addition to estimating coverage, the investigators were interested in the descriptive epidemiology of measles occurrence in Muyinga specifically, and in Burundi generally.

Question 9: What sources of information might be used to describe measles occurrence in Muyinga and Burundi?

PART II – Surveillance

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

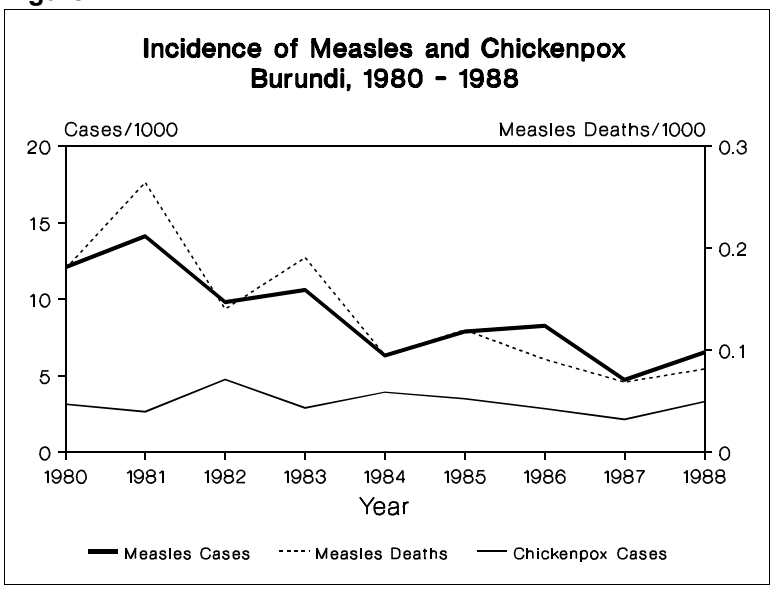
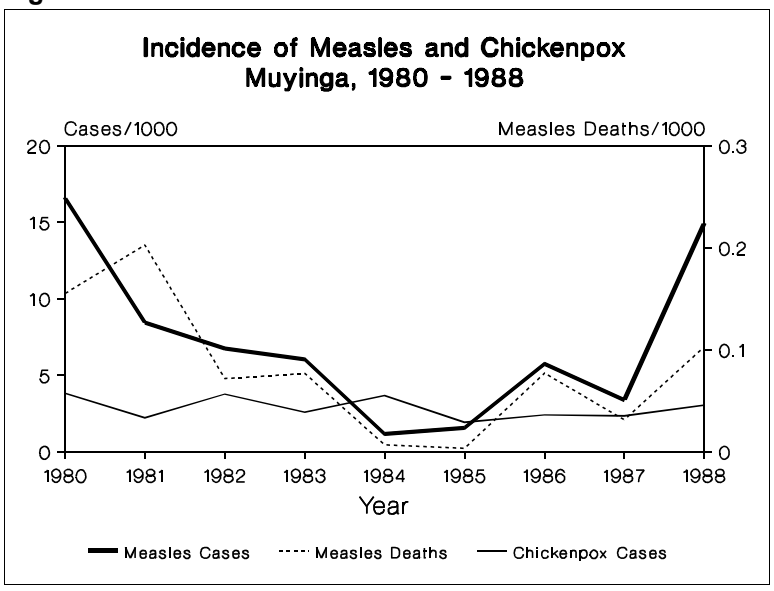
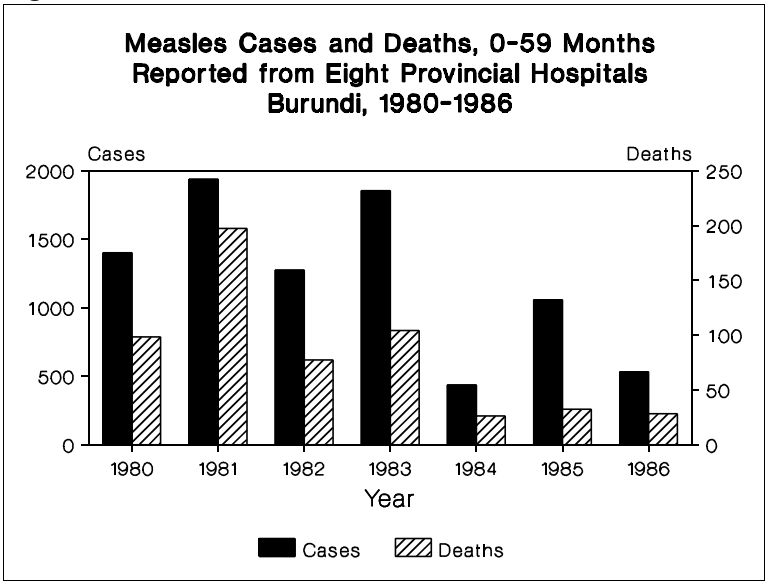


Figure 5



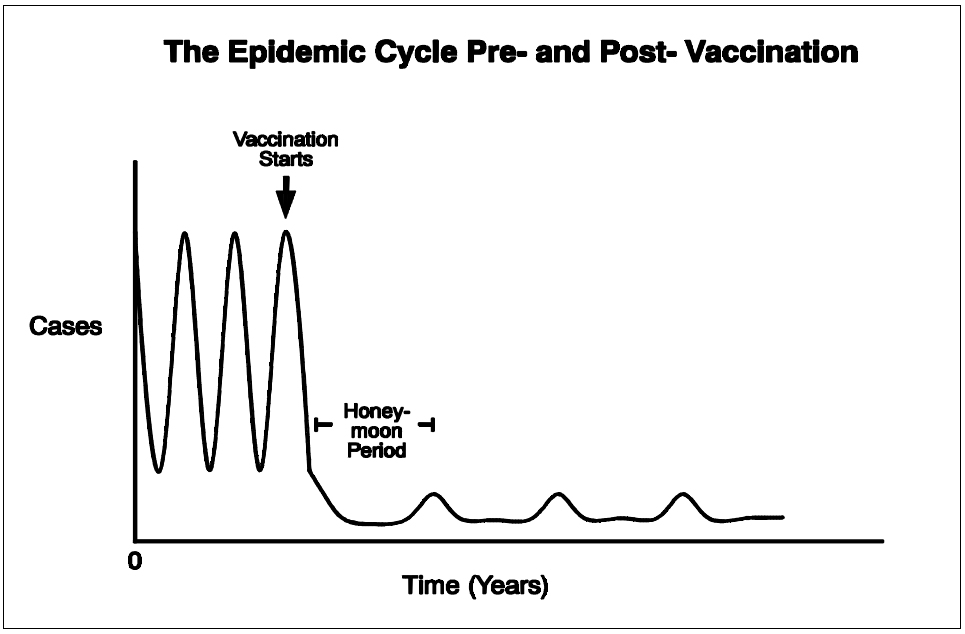
A recently completed study based on the registries of the eight major provincial hospitals provided additional data on persons admitted to hospitals for measles and deaths from measles, summarized in Figure 6.

Figure 6



Question 10: Describe and interpret the trends in measles morbidity and mortality in Burundi.

If you look closely at Figure 4, you will note peaks in the incidence of measles every couple of years. Figure 7 represents an idealized epidemic cycle of measles in a rural region before and after the introduction of measles vaccination.



Question 11: Why do certain communicable diseases such as measles have regular epidemic cycles?

PART III - Vaccine Efficacy

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, 1984–1988.

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

Table 8. Hypothetical populations with vaccine coverage of 0%, 20%, 60%, and 100%.

	Population			
	A	B	C	D
a. Number of persons in population	100	100	100	100
b. Vaccine efficacy (VE)	90%	90%	90%	90%
c. Percent population vaccinated (PPV)	0%	20%	60%	100%
d. Number vaccinated (a × c)	_____	20	_____	_____
e. Number unvaccinated (a ! d)	_____	80	_____	_____
f. Number protected (d × b)	_____	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%	_____	_____

Consider the use of a vaccine with 90% efficacy in four different hypothetical populations of 100 people each, with vaccine coverage of 0%, 20%, 60%, and 100%, respectively. Assume that every unvaccinated person will be exposed to, and will develop, measles.

Question 13: Complete Table 8.

Question 14: What do you conclude about the relationship between coverage and number of cases vaccinated?

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. Such field assessments 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 investigators conducted a door-to-door census 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):

Table 9a. Measles cases by vaccination status, Muyinga, survey, January 1989 – All children in census (measles cases as reported by mother; children without vaccination card counted as unvaccinated)

Vaccination Status	Measles	No measles	Total	Attack rate
Vaccinated	109	843	952	**ARV** = 109 / 952 = 11.4%
Unvaccinated	182	607	789	**ARU** = 182 / 789 = 23.1%
Total	291	1,450	1,741	

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

Question 15: Using the data in Tables 9b-9d, calculate the ARV, ARU, and vaccine efficacy for each table. Discuss the reasons for the differing results obtained.

Table 9b. Measles cases by vaccination status, Muyinga, survey, January 1989 – Unvaccinated children restricted to those with vaccination cards (on which there is no record of measles vaccination).

Vaccination Status	Measles	No measles	Total	Calculations
Vaccinated	109	843	952	**ARV =** _____
Unvaccinated	121	309	430	**ARU =** _____
Total	230	1,152	1,382	**VE =** _____

Table 9c. Measles cases by vaccination status, Muyinga, survey, January 1989 – 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.

Vaccination Status	Measles	No measles	Total	Calculations
Vaccinated	49	843	892	**ARV =** _____
Unvaccinated	59	309	368	**ARU =** _____
Total	108	1,152	1,260	**VE =** _____

Table 9d. Measles cases by vaccination status, Muyinga, survey, January 1989 – Same criteria in Tables 9b and 9c and analysis restricted to children $ 9 months of age.

Vaccination Status	Measles	No measles	Total	Calculations
Vaccinated	48	840	888	**ARV =** _____
Unvaccinated	44	116	160	**ARU =** _____
Total	92	956	1,048	**VE =** _____

Question 16: Define vaccine efficacy in common English.

PART IV - Conclusion

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.

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 EPI programs!

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.

To prevent future buildup of susceptibles in Burundi, EPI program managers decided to maintain the primary focus of the program on 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.

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 accination 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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