AFRICA CHILD SURVIVAL INITIATIVE

COMBATTING CHILDHOOD COMMUNICABLE DISEASES

(ACSI-CCCD)

EPIDEMIOLOGY CASE STUDY: A MEASLES OUTBREAK

UNITED STATES AGENCY FOR INTERNATIONAL DEVELOPMENT
Africa Regional Project (698-0421)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
and Prevention
International Health Program Office

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

A Case Study and Training Exercise for EPI Managers Revised April 1993

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

This is an exercise in assessing vaccination coverage, interpreting measles surveillance information, estimating vaccine efficacy, and discussing measles control strategies. This exercise uses real data from a measles outbreak investigation in Health Sector Muyinga, Burundi, 1989.

PART 1 - VACCINATION COVERAGE

Objective: To discuss methods for evaluating vaccination coverage, including their advantages and disadvantages.

Description: Describes the background vaccination program and the situation of a suspected measles outbreak, bringing vaccination coverage into question. Participants will: review the principle of the administrative method (doses Administered/target Population), with an example and exercise using Burundi figures; compare results with estimates from Convenience Sample Surveys and EPI 30-Cluster Surveys; briefly review principle advantages and disadvantages of each method (1 hour).

PART II - DISEASE SURVEILLANCE

Objective: To interpret surveillance data to assess the impact of vaccination programs. To describe the role of susceptibles and immunes in epidemic cycles, and the changes induced by a vaccination program.

Description: Provides graphs showing trends of measles incidence, measles mortality, and chickenpox incidence, for Burundi and Health Sector Muyinga, 1980-1988. Provides age distribution figures for 1985-1988. Participants will: interpret trends in measles incidence and the effect of vaccination, showing decreasing incidence and widening inter-epidemic period, then occurrence of a "post-honeymoon" outbreak; discuss the role of accumulation of susceptibles in epidemic cycles; interpret changes in age-distribution, with relative shift towards younger and older age-groups. (1 1/2 hours).

PART II, Optional - DISEASE SURVEILLANCE

Objective: To use surveillance data to calculate, graphically represent, and interpret incidence and mortality rates.

Description: Provides raw surveillance data on measles reported cases and deaths, chickenpox reported cases, and population figures, for Burundi and Muyinga, 1980-1988. Participants will: calculate incidence rates; draw the corresponding graphs; interpret trends as in Part II, above. (2 hours).

PART III - VACCINE EFFICACY

Objectives: To describe methods to estimate vaccine efficacy and discuss their most common biases.

Description: Describes basic formula for vaccine efficacy in cohort studies. Provides attack rates by vaccination status from a cohort study in Muyinga. Participants will: discuss the meaning of an increased proportion of vaccinated persons among cases; complete a simple table with ex-

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amples using hypothetical figures; calculate vaccine efficacy in 4 different situations, illustrating biases induced by assessment of disease status, assessment of vaccination status, and selected age groups; estimate vaccine efficacy with the screening method; and compare results with those obtained from the cohort study. (1 1/2 to 2 hours).

PART IV - MEASLES CONTROL

Objective: To discuss options for measles control strategies, with emphasis on selection of appropriate target age-groups.

Description: Provides data on age-specific attack rates, age-specific mortality, and secondary transmission, from a census study in Muyinga. Participants will: discuss optimal target age-groups for measles vaccination; discuss options of preventing "post-honeymoon" outbreaks and minimizing their impact. (1 hour).

Part IV is optional. If time is limited, or if participants have no experience with measles control strategies in the context of EPI, Questions 15-18 can be skipped and participants can proceed to Part V - Conclusions.

PART V - CONCLUSIONS

Objective: To wrap-up the exercise with an overview of the principles of measles control and the rationale for various options and strategies.

Description: Part V is made of the answers to Questions 15-18 in Part IV (see above). Participants will read Part V as conclusion to the exercise session. (20 minutes).

INSTRUCTOR'S GUIDE

Provides completed tables and graphs (which can be used as overheads to save time during discussions), and an outline of the answers to all questions.

Recommended Formats

Short version (one session, duration approx. 4 hours):

Parts I, II, and III, read Part V.

Recommended if time is limited, or if participants have no experience with measles control issues in the context of EPI.

Medium version (one 5-hour session, or preferably two 3-hour sessions):

Parts I and II (2 to 3 hours).
Parts III and IV (3 hours).

Recommended, if time and interest of participants allow a discussion of measles control strategies
(Part IV).

Long version (two 3-hour sessions):

Session 1: Parts I and II, Optional (3 to 4 hours).
Session 2: Parts III and IV (3 hours).

Recommended if the exercise is used to practice calculation of incidence rates and drawing graphs (Part II, Optional). The two sessions can be scheduled for two different time periods

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Instructor's Guide

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

INSTRUCTOR'S GUIDE

NOTE 1: The five parts of the exercise should be distributed separately; blank pages have been inserted in the exercise document to allow the five parts to be copied two-sided. *Do not remove* the blank pages from the exercise before reproducing for distribution.

NOTE 2: *Questions 15-18* in *Part IV* are optional; if the exercise is covered in a single session and time is limited, or if participants have little or no experience with management of EPI programs, we suggest skipping *Questions 15-18*, and have the group directly read the *Part V - CONCLUSIONS* section (which is identical to *Answers 15-18* in the Instructor's Guide).

NOTE 3: *Part II, Optional* is an alternative to *Part II*. Instead of providing the participants with graphs of surveillance data, *Part II, Optional* provides crude surveillance and population figures and an opportunity to calculate incidence and mortality rates and draw the corresponding graphs; to use *Part II, Optional*, remove *Part II* from the exercise and from the Instructor's Guide, and replace it with *Part II, Optional*; *Part II, Optional* will take more time than *Part II*; if *Part II, Optional* is used, we suggest dividing the exercise into two sessions, one session covering *Part I* and *Part II, Optional* and one session covering *Parts III, IV*, and *V*.

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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Instructor's Guide

Part I
Vaccination Coverage

[redacted]

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

PART I - VACCINATION COVERAGE

QUESTION 1:

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

ANSWER 1:

Given that the credibility of EPI has been brought into question by the outbreak, data that are readily available (e.g., collected through routine surveillance or past special studies) need to be quickly analyzed and presented (with the appropriate caveats) to blunt the initial criticisms. This done, there is then time to design and conduct special studies to examine hypotheses raised by this initial review.

The initial review should focus on:

- data on measles-vaccine coverage to verify that coverage has in fact been improving. However, high overall coverage can hide large pockets of low coverage.

- measles surveillance data to describe morbidity and mortality trends over time.

- methodology used to obtain the above information, potential biases, and whether independent sources of data are available to validate or refute these data.

It is in situations such as this one that the availability of good routine surveillance data and good record keeping is invaluable — both tasks that may otherwise appear mundane and unexciting.

QUESTION 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).

ANSWER 2:

Table 1. Surviving infants in Burundi

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	235,200	24,696	210,504

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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	13,776	1,446	12,330
1987	322,000	15,456	1,623	13,833

QUESTION 3:
Estimate the measles vaccination coverage in Burundi in 1988 and in Health Sector Muyinga in 1984 and 1988.

ANSWER 3:
Table 3. Measles vaccination coverage, Burundi

Year	Doses administered 9-11 mo (Y-1)	Doses administered 12-23 mo (Y) +9-11 mo (Y-1)	Surviving infants born Year (Y-1)	Coverage by Age 1	Coverage by Age 2
1984	52,539	90,020	189,024	28%	48%
1986	84,664	110,436	201,912	42%	55%
1988	145,528	138,140	210,504	69%	66%

Table 4. Measles vaccination coverage, Health Sector Muyinga

Year	Doses administered 9-11 mo (Y-1)	Doses administered 12-23 mo (Y) +9-11 mo (Y-1)	Surviving infants born Year (Y-1)	Coverage by Age 1	Coverage by Age 2
1984	4,206	5,430	12,330	34%	44%
1988	7,142	9,450	13,833	52%	68%

Discussion points: As most infant mortality occurs before the age for measles vaccination, the number of surviving infants is commonly used to approximate the size of the target population for measles vaccination programs.

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

ANSWER 4:

Administrative method

Advantages: Very good if good numerators and good denominators; data readily available; enable vaccination personnel to monitor their performance monthly, and at the local level; cheap; no disruption in other activities; no need for quality records at individual vaccinee level, just at level of office with such records; standardized method permits combining data from regions to develop aggregate estimates.

Disadvantages: Requires some basic arithmetic; population denominators frequently inaccurate, especially at the local level; problems with numerators if changes in target age, or changes in percentage between 9- to 11-month-olds versus 12- to 23-month-olds, or if reports of doses administered are incomplete or inaccurate.

Convenience sample surveys

Advantages: Quick, can target easily defined populations (e.g., health center, market, village X).

Disadvantages: Questionable accuracy, likely to be biased toward higher coverages as convenient for survey team; probably means population with easier access to health-care services.

EPI 30-cluster surveys

Advantages: Standardized method available, reasonably simple; very useful when nothing else is available, especially when denominator data are lacking for "Administrative Method"; useful to validate the "Administrative Method."

Disadvantages: Expensive and disruptive; requires fuel and transport to reach distant villages for sampling; usually EPI staff are pulled from routine job to participate on the surveys (usually about 2 weeks' duration); accuracy depends on availability of vaccination records of persons sampled; requires list of villages and their populations as sampling frame for first stage (does not matter whether list is out of date; what matters is the relative population of villages, to ensure selection proportionate to size); does not provide information at the local level.

The comparison of the coverage by study method shows that, as expected, the coverage based on convenience sample for Muyinga is much higher than that using the "Administrative Method." In contrast, the coverage for Burundi using the EPI 30-cluster method correlates well with that of the "Administrative Method," suggesting the latter is a good proxy for the true coverage.

Instructor's Guide

Part II
Disease Surveillance

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

PART II - DISEASE SURVEILLANCE

QUESTION 5:

Describe and interpret the trends in measles morbidity and mortality in Burundi and Health Sector Muyinga.

ANSWER 5:

Burundi: From 1980 through 1988, even taking the 1988 outbreak into account, both measles morbidity and mortality have been reduced by approximately half (from 12.1/1,000 to 6.2/1,000 and from 0.18/1,000 to 0.08/1,000, respectively). Epidemic peaks of January 1981, February 1983, January 1986, and December 1988 suggest lengthening of interepidemic period from every 25 months to every 35 months.

Muyinga: From 1980 through 1987, before the 1988 outbreak, both measles morbidity and mortality were reduced by four-fifths (from 16.6/1,000 to 3.4/1,000 and from 0.16/1,000 to 0.03/1,000, respectively). The 1988 epidemic is the first major epidemic since 1980, suggesting an interepidemic period of 8 years in duration (minor epidemics in 1983 and 1986). Data before 1980 are not available to use in a comparison, but such a long interepidemic period is unusual in developing countries. This probably reflects Muyinga's higher vaccine coverage, especially its successful mass campaign in 1981.

Persons hospitalized with measles tend to have more severe disease and better access to health-care services. But in general, this trend should reflect overall measles incidence. They also show a decline in morbidity and mortality, thereby serving as another independent source of validation for the routine surveillance data.

QUESTION 6:

Use data on chickenpox incidence in Figures 3-4 to discuss the validity of the trends in measles incidence observed via routine surveillance.

ANSWER 6:

Chickenpox is another highly infectious disease with good specificity of diagnosis by primary health-care workers. Since there are currently no interventions against chickenpox, the true incidence of chickenpox should be fairly constant over time. An accurate surveillance system should reflect this constancy. Both the Burundi and Muyinga data do in fact show this constancy of chickenpox incidence. One can conclude therefore that the decline in measles morbidity and mortality observed via routine surveillance are probably real and not simply artifacts of underreporting.

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

ANSWER 7:
On the basis of the above data, one can conclude that measles morbidity and mortality have been dramatically reduced since measles vaccination was introduced in 1981. Furthermore, the interepidemic period has been lengthened. Even with the 1988 epidemic, EPI has had a major impact on measles control in Burundi.

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

ANSWER 8:
The epidemic cycles result from the continuous addition of susceptibles to a population via its newborns (who become susceptible after the waning of their maternal antibodies) or via immigration. These new susceptibles accumulate until the "critical mass" for an outbreak is reached (in mathematical modeling terminology, when the *net reproductive rate* [also called the basic reproductive rate/ratio] exceeds one, i.e., on average, one infected person infects another susceptible person before the end of their infectious period). After the outbreak, most susceptibles have become immune. The newborns slowly replenish the pool of susceptibles until critical mass is reached, and the cycle repeats itself.

The epidemic subsides when the net reproductive rate falls below one. Note that this occurs before every single susceptible is infected. This is the basis for "herd immunity." The remaining susceptibles are "protected," not by their own immunity, but by the fact that there are enough immunes in the community to prevent transmission from sustaining itself (i.e., not enough susceptibles to sustain transmission). Reproductive rates vary by disease—very low for smallpox and very high for measles. Diseases with low reproductive rates are easier to eradicate.

QUESTION 9:
In rural areas, the introduction of a vaccination program generally results in a lengthening of the period between measles epidemics (Figure 6). Can you explain why?

ANSWER 9:
The "natural" equilibrium of measles epidemics can be disturbed by changes in a) rate of introductions of susceptibles or b) contact rate between susceptibles and infected. Vaccination should convert susceptibles to immunes, thereby slowing the accumulation of susceptibles. However, for highly contagious diseases such as measles, an epidemic will still occur when the critical mass of susceptibles is reached. This delay in accumulation of susceptibles manifests in a lengthening of the interepidemic period. In urban settings, person-to-person contact rates are so high that susceptibles do not accumulate to the same degree as in rural areas, and lengthening of the interepidemic period is generally not observed unless very high coverage levels are attained.

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

ANSWER 10:
Children in the main age group eligible for measles vaccination (12-23 months of age) constitute a smaller and smaller proportion of the remaining cases, while younger (0-11 months of age) and older (24+ months of age) children constitute a growing proportion. Note that vaccination changes the age distribution of the remaining measles cases, but the total number of measles cases overall is still declining until 1987 in Burundi (Figures 3 & 5), and until 1984 in Muyinga (Figure 4). After 1984 in Muyinga, the total number of cases increases, mostly as a result of cases in age-groups out of the target age for vaccination. The analogy is squeezing a leaking balloon in the middle, which bulges on the two sides of the squeeze, the "older" side more than the "younger" side (time permitting, graph on board the data from Table 8, or show a transparency with Figures 7-8). The lengthening of the interepidemic period permits larger numbers of susceptibles to reach older ages than in the prevaccination era. Therefore, once the epidemic hits, more of the cases are among the older age groups. Without a special program to target this "bulge" of older susceptibles moving through the population, this shift in age distribution of cases would continue. In the United States, many of the measles outbreaks are in high schools and colleges. Anecdotally, persons as old as 20 years of age with measles as old were reported in Muyinga in 1988.

The ever-increasing *proportions* of measles patients 0-11 months of age and 24+ months of age are due to a slower decline in measles incidence (no vaccination before 9 months or after 23 months and lower coverage in early years of the vaccination program, resulting in lower coverage for older age groups) compared with a more rapid decline in incidence among 12- to 23-month-olds (entire age group being vaccinated with high coverage). If month-specific data were available, a more ideal age grouping to examine the change in age distribution for measles would have been 0-8 months vs. 9-23 months vs. 24+ months [NOTE: Ideally, to adequately describe the trends in incidence by age, one would need population denominators by age groups to calculate age-specific incidence rates].

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FIGURE 7

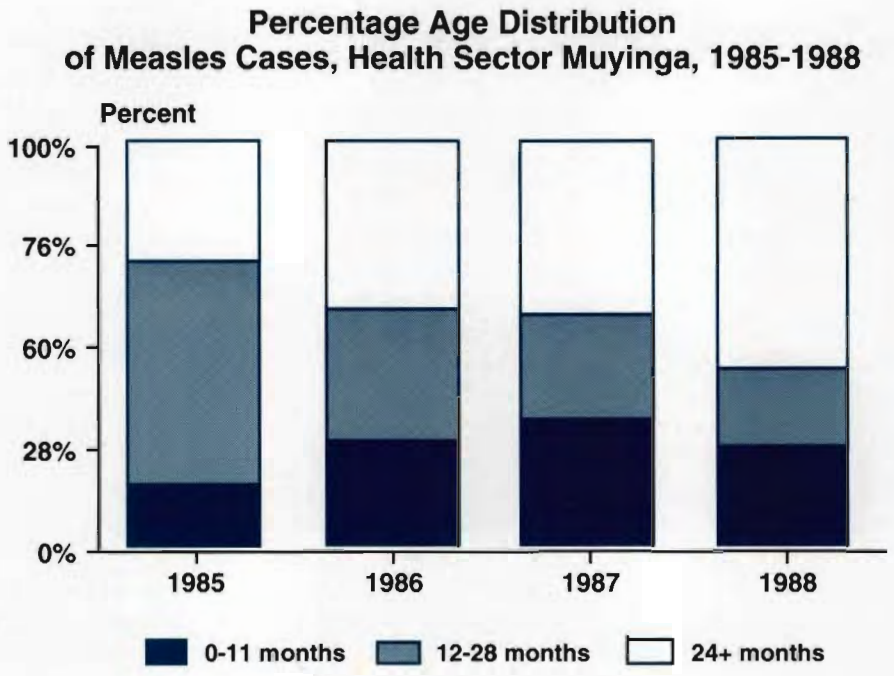
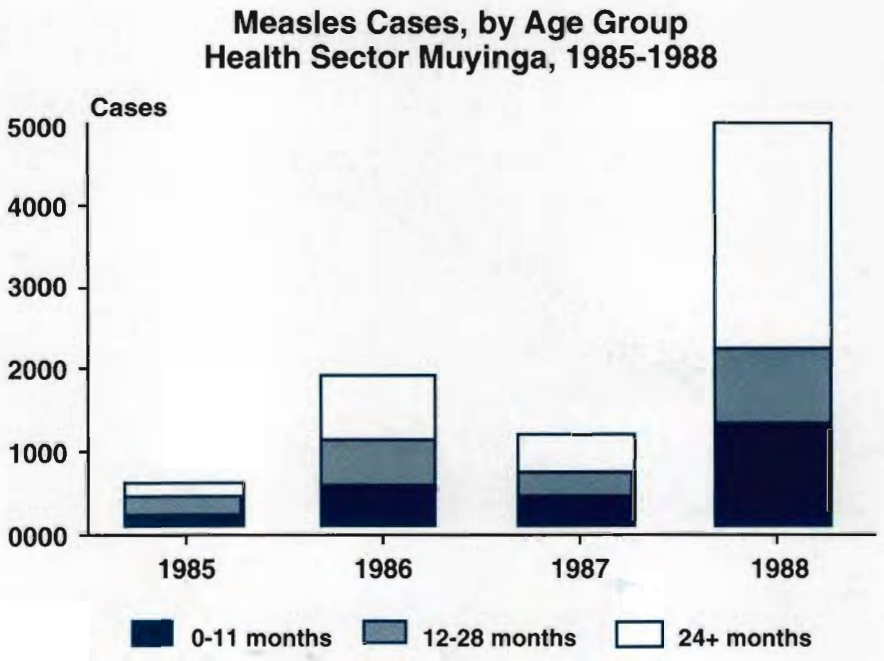


FIGURE 8



Instructors Guide

Optional Part II

A MEASLES OUTBREAK IN A HIGHLY VACCINATED POPULATION: HEALTH SECTOR MUYINGA, BURUNDI, 1988-1989

PART II, OPTIONAL - DISEASE SURVEILLANCE

QUESTION 5A:

Using Tables 7 and 8, calculate measles incidence, measles mortality, and chickenpox incidence rates for Burundi and Health Sector Muyinga, 1980-1988. Figures for 1980 are given as example.

Table 7: Total Population, Measles and Chickenpox Cases and Measles Deaths, Burundi, 1980-1988.

YEAR	1980	1981	1982	1983	1984	1985	1986	1987	1988
POPULATION X 1000	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	14.04	9.78	10.62	6.35	7.82	8.25	4.75	6.50
MEASLES DEATHS/1000	0.18	0.26	0.14	0.19	0.10	0.12	0.09	0.07	0.08
CHICKENPOX CASES/1000	3.12	2.63	4.74	2.90	3.93	3.48	2.84	2.15	3.31

Table 8: Total Population, Measles and Chickenpox Cases and Measles Deaths, Health Sector Muyinga, 1980-1988.

YEAR	1980	1981	1982	1983	1984	1985	1986	1987	1988
POPULATION X 1000	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	8.41	6.74	6.00	1.15	1.54	5.72	3.37	14.70
MEASLES DEATHS/1000	0.16	0.20	0.07	0.08	0.01	0.00	0.08	0.03	0.10
CHICKENPOX CASES/1000	3.81	2.20	3.74	2.56	3.66	1.90	2.40	2.33	3.04

QUESTION 5B:
Draw the corresponding graphs (Figures 3-4).

FIGURE 3

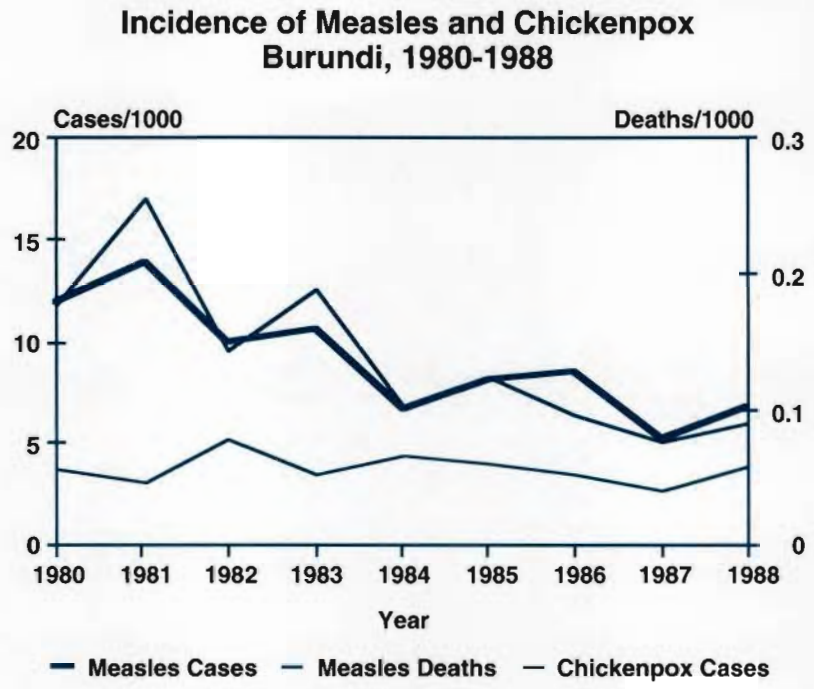
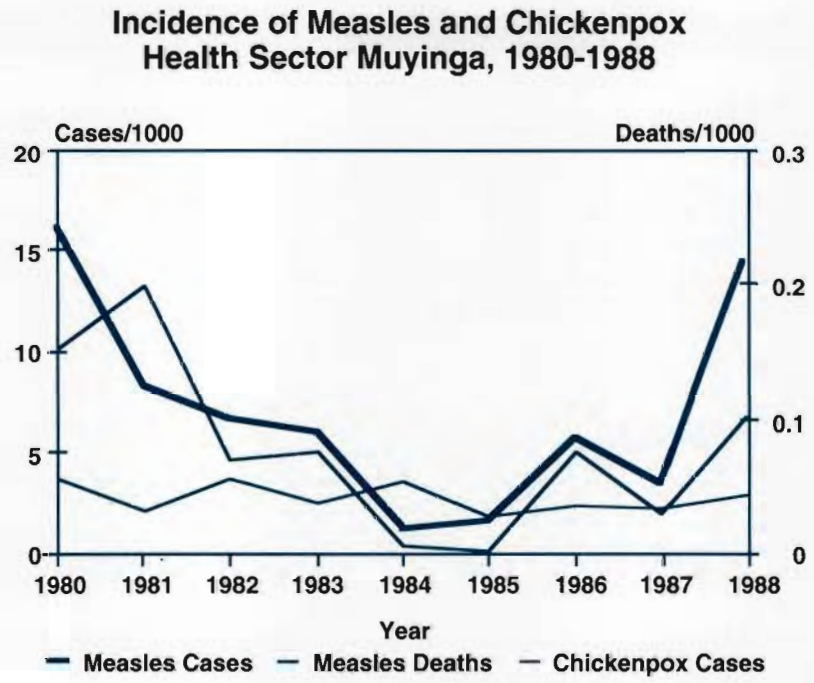


FIGURE 4



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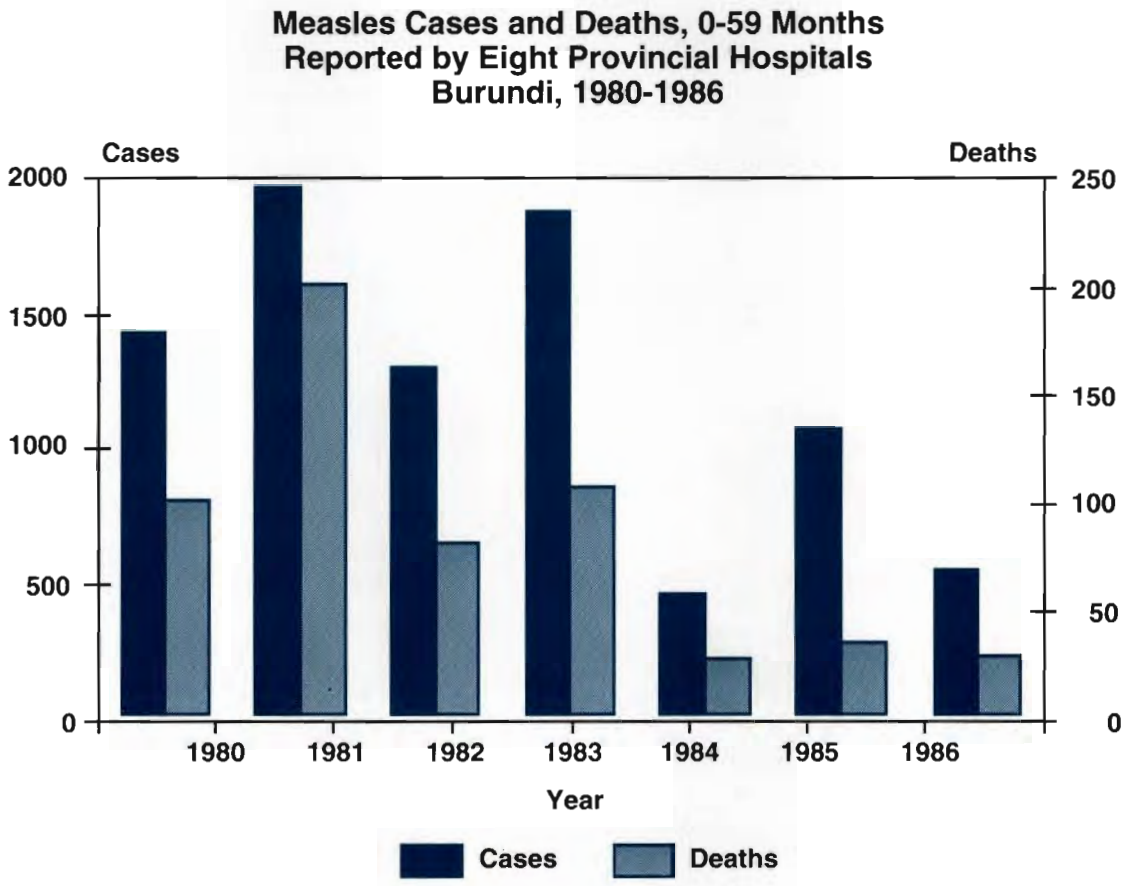
QUESTION 5c:
Represent on a graph (Figure 5) the data on measles cases and measles deaths in hospitals presented in Table 9.

FIGURE 5



QUESTION 5D:
Using Figures 3-5, describe and interpret the trends in measles morbidity and mortality in Burundi and Health Sector Muyinga.

ANSWER 5D:
Burundi: From 1980 through 1988, even taking the 1988 outbreak into account, both measles morbidity and mortality have been reduced by approximately half (from 12.1/1,000 to 6.2/1,000 and from 0.18/1,000 to 0.08/1,000, respectively). Epidemic peaks of January 1981, February 1983, January 1986, and December 1988 suggest lengthening of interepidemic period from every 25 months to every 35 months.

Muyinga: From 1980 through 1987, before the 1988 outbreak, both measles morbidity and mortality were reduced by four-fifths (from 16.6/1,000 to 3.4/1,000 and from 0.16/1,000 to 0.03/1,000, respectively). The 1988 epidemic is the first major epidemic since 1980, suggesting an interepidemic period of 8 years in duration (minor epidemics in 1983 and 1986). Data before 1980 are not available to use in a comparison, but such a long interepidemic period is unusual in developing countries. This probably reflects Muyinga's higher vaccine coverage, especially its successful mass campaign in 1981.

Persons hospitalized with measles tend to have more severe disease and better access to health-care services. But in general, their trends should reflect overall measles incidence. They also show a decline in morbidity and mortality, thereby serving as another independent source of validation for the routine surveillance data.

QUESTION 6:

Use data on chickenpox incidence in Figures 3-4 to discuss the validity of the trends in measles incidence observed via routine surveillance.

ANSWER 6:

Chickenpox is another highly infectious disease with good specificity of diagnosis by primary health-care workers. Since there are currently no interventions against chickenpox, the true incidence of chickenpox should be fairly constant over time. An accurate surveillance system should reflect this constancy. Both the Burundi and Muyinga data do in fact show this constancy of chickenpox incidence. One can conclude therefore that the decline in measles morbidity and mortality observed via routine surveillance are probably real and not simply artifacts of underreporting.

QUESTION 7:

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

ANSWER 7:

On the basis of the above data, one can conclude that measles morbidity and mortality have been dramatically reduced since measles vaccination was introduced in 1981. Furthermore, the interepidemic period has been lengthened. Even with the 1988 epidemic, EPI has had a major impact on measles control in Burundi.

QUESTION 8:

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

ANSWER 8:

The epidemic cycles result from the continuous addition of susceptibles to a population via its newborns (who become susceptible after the waning of their maternal antibodies) or via immigration. These new susceptibles accumulate until the "critical mass" for an outbreak is reached (in mathematical modeling terminology, when the net reproductive rate exceeds one, i.e., on average, one infected person infects another susceptible person). After the outbreak, most susceptibles have become immune. The newborns slowly replenish the pool of susceptibles until critical mass is reached, and the cycle repeats itself.

The epidemic subsides when the net reproductive rate falls below one. Note that this occurs before every single susceptible is infected. This is the basis for "herd immunity." The remaining susceptibles are "protected," not by their own immunity, but by the fact that there are enough immunes in the community to prevent transmission from sustaining itself. Reproductive rates vary by disease—very low for smallpox and very high for measles. Diseases with low reproductive rates are easier to eradicate.

QUESTION 9:

In rural areas, the introduction of a vaccination program generally results in a lengthening of the period between measles epidemics (Figure 6). Can you explain why?

ANSWER 9:

The "natural" equilibrium of measles epidemics can be disturbed by changes in a) rate of introduction of susceptibles or b) contact rate between susceptibles and infected. Vaccination converts susceptibles to immunes, slowing the accumulation of susceptibles. However, for highly contagious diseases such as measles, an epidemic will still occur when the critical mass of susceptibles is reached. This delay in accumulation of susceptibles is manifested by a lengthening of the interepidemic period. In urban settings, person-to-person contact rates are so high that susceptibles do not accumulate to the same degree as in rural areas, and lengthening of the interepidemic period is generally not observed unless very high coverage levels are attained.

QUESTION 10A:

Using data from Table 6, represent graphically the percentage age distribution of measles cases (Figure 7) and the measles cases by age group (Figure 8).

ANSWER 10A:

Figures 7 and 8.

QUESTION 10B:

Using Figures 7-8, describe and interpret the changes in the age distribution of measles cases in Muyinga.

ANSWER 10B:

Children in the main age group eligible for measles vaccination (12-23 months of age) constitute a smaller and smaller proportion of the remaining cases, while younger (0-11 months of age) and older (24+ months of age) children constitute a growing proportion. Note that vaccination changes the age distribution of the remaining measles cases, but the total number of measles cases overall is still declining until 1987 in Burundi (Figures 3,5), and until 1984 in Muyinga (Figure 4). The analogy is squeezing a leaking balloon in the middle, which bulges on the two sides of the squeeze, the "older" side more than the "younger" side. (time permitting, graph on board the data from Table 6, or show a transparency with Figure 8). The lengthening of the interepidemic period permits larger numbers of susceptibles to reach older ages than in the prevaccination era. Therefore, once the epidemic hits, more of the cases are among the older age groups. Without a special program to target this "bulge" of older susceptibles moving through the population, this shift in age distribution of cases would continue. In the United States, many of the measles outbreaks are in high schools and colleges. Anecdotally, persons as old as 20 years of age with measles were reported in Muyinga in 1988.

The ever-increasing *proportions* of measles patients 0-11 months of age and 24+ months of age are due to a slower decline in measles incidence (no vaccination before 9 months or after 23 months and lower coverage in early years of the vaccination program, resulting in lower coverage for older age-groups) compared with a more rapid decline in incidence among 12- to 23-month-olds (entire age group being vaccinated with high coverage). If month-specific data were available, a more ideal age grouping to examine the change in age distribution for measles would have been 0-8 months vs. 9-23 months vs. 24+ months [NOTE: Ideally, to adequately describe the trends in incidence by age, one would need population denominators by age groups to calculate age-specific incidence rates].

FIGURE 7

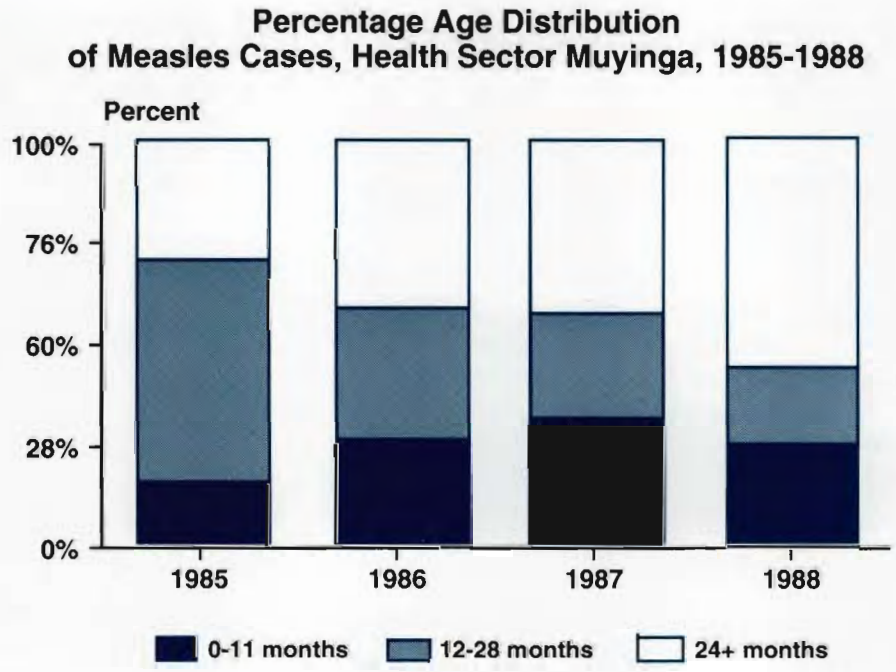


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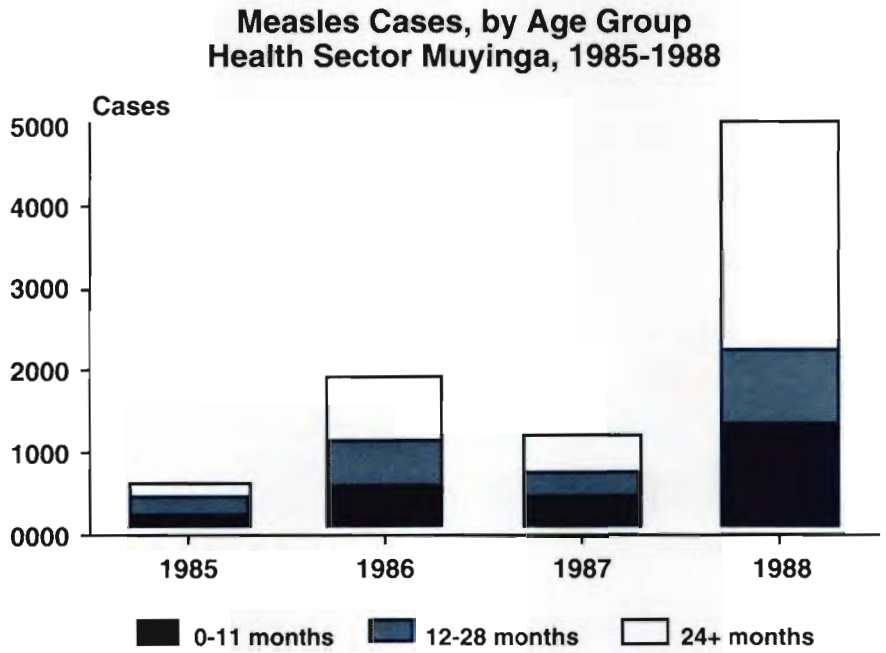
FIGURE 8


Measles Cases, by Age Group
Health Sector Muyinga, 1985-1988
Cases
5000
4000
3000
2000
1000
0000
1985
1986
1987
1988
0-11 months
12-28 months
24+ months

Instructor's Guide

Part III
Vaccine Efficacy

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A-MEASLES OUTBREAK IN A HIGHLY VACCINATED POPULATION: HEALTH SECTOR MUYINGA, BURUNDI, 1988-1989

PART III - VACCINE EFFICACY

QUESTION 11:

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

ANSWER 11:

No. The increase in proportion of persons with measles who have a history of vaccination can be due either to a) poor efficacy or b) normal efficacy combined with increasing vaccine coverage. A vaccine-efficacy study is needed to determine which factor is predominant.

For any vaccine that is not 100% effective, some persons who have been vaccinated will later acquire measles. The percentage of cases vaccinated (PCV) is directly related to the percentage of population vaccinated (PPV) (i.e., vaccine coverage). See Question 12.

QUESTION 12:

Table 11 provides the data needed to calculate the Percentage of 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. Complete Table 11. What can you conclude about the relationship between coverage and number of cases vaccinated?

ANSWER 12:

Table 11. Hypothetical populations with vaccine coverage of 20%, 60%, and 100%

a. Total population	100	100	100
b. Vaccine efficacy (VE)	90%	90%	90%
c. Percentage population vaccinated (PPV)	20%	60%	100%
d. Number vaccinated (axc)	20	**60**	**100**
e. Number unvaccinated (ill) (a-d)	80	**40**	**0**
f. Number protected (dxb)	18	**54**	**90**
g. Number vaccinated but ill (d-f)	2	**6**	**10**
h. Total number ill (e+g)	82	**46**	**10**
i. Percentage cases vaccinated (PCV) (g/h)	2.4%	**13%**	**100%**

Note the apparently paradoxical result of higher coverage leading to higher PCV. In fact, if 100% children were immunized (PPV = 100%), all cases would be in vaccinated children (PCV = 100%).

QUESTION 13:
Using the equation provided above, calculate the vaccine efficacy for Tables 12B-12D (calculations for Table 12A are given as example). Discuss the reasons for the differing results obtained.

ANSWER 13:
Table 12A. All children in census (measles cases as reported by mother; children without vaccination card counted as unvaccinated)

	Measles	No measles	Total
Vaccinated	115	893	1,008
Unvaccinated	207	685	892
Total	322	1,578	1,900

ARU = 207/892 = 23% ARV = 115/1,008 = 11%

VE = (23% - 11%) / 23% = 1 - (11% / 23%) = 51%

Table 12B. Unvaccinated children restricted to those with vaccination cards (on which there is no record of measles vaccination)

	Measles	No measles	Total
Vaccinated	115	893	1,008
Unvaccinated	122	316	438
Total	237	1,209	1,446

ARU = 122/438 = 28% ARV = 115/1008 = 11%

VE = (28% - 11%) / 28% = 1 - (11% / 28%) = 61%

Table 12C. Criteria in 12B + measles patients 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	50	893	943
Unvaccinated	60	316	376
Total	110	1,209	1,319

ARU = 60/376 = 16% ARV = 50/943 = 5%

VE = (16% - 5%) / 16% = 1 - (5% / 16%) = 69%

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

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Table 12D. Criteria in 12B + 12C + analysis restricted to children ≥9 months of age

	MEASLES	NO MEASLES	TOTAL
VACCINATED	41	701	742
UNVACCINATED	31	118	149
TOTAL	72	819	891

ARU = 31/149 = 21% ARV = 41/742 = 6%

VE = (21% - 5%) / 21% = 1 - (5% / 21%) = 73%

Vaccine efficacy calculations depend critically on accurate classification of vaccination status and disease status.

Comparison between Table 12A and Table 12B shows the impact on VE of misclassification regarding the vaccination status. Recall that interviewers recorded vaccinations only if they were documented on cards. Under this method of data collection, children who had lost their cards would be counted as "unvaccinated" even if they had been vaccinated (Table 12A). This would falsely increase the number of unvaccinated, resulting in a falsely low attack rate among the unvaccinated (23% instead of 28%), and falsely low vaccine efficacy (51% instead of 61%). (In Table 12B, only children with a card, but with no record of measles vaccination on it, were counted as unvaccinated).

Comparison between Table 12B and Table 12C shows the impact on VE of misclassification of measles disease status. In Tables 12A and 12B, the interviewers accepted the mother's diagnosis that her child had measles during the epidemic. There was no laboratory confirmation that the child actually had measles and not another febrile illness that was misdiagnosed by the mother as measles. Since measles vaccine cannot be expected to protect against a non-measles illness, this results in falsely high attack rates in both vaccinated and unvaccinated, more so in the vaccinated, the end result being a falsely low VE (61% instead of 69%).

Comparison between Table 12C and Table 12D shows the impact on VE of misclassification of measles susceptibility status. Infants are usually protected against measles during the first 6-12 months of life because of transplacental maternal antibodies. The infants become susceptible to measles when these maternal antibodies have waned. Unfortunately, the residual maternal antibodies also interfere with measles vaccine seroconversion and efficacy. This is why measles vaccination was delayed until 9 months of age. Measles vaccine efficacy depends critically on the age of administration. VE is generally 80%-85% when administered at 9 months of age and 95%-98% when administered at 15 months of age.

Compared with Table 12C, Table 12D includes only children ages 9-59 months of age, and excludes: a) unvaccinated children <9 months of age who falsely lower the attack rate among the unvaccinated because most of them are still protected by maternal antibodies, and b) vaccinated children <9 months of age who falsely elevate the attack rate among the vaccinated because measles vaccination at such a young age is less effective. Together, they result in a falsely low VE (69% instead of 73%). The residual difference between the VE found in our study (73%) and the seroconversion studies (80-85%) may be due to 1) ineffective vaccine from breaks in the cold chain and/or 2) residual bias in study design not adequately controlled for (e.g., more unvaccinated may have had measles in past years than the vaccinated).

Thus we conclude a) the VE in Muyinga was close to the expected limits given the target age of administration and b) the increase in proportion of cases vaccinated is due primarily to normal efficacy and increasing coverage and not to poor vaccine efficacy.

[Optional discussion point: Some authors make a distinction between vaccine *efficacy* and vaccine *effectiveness*; "Efficacy" usually refers to estimates from controlled prospective trials, while "effectiveness" refers to estimates obtained from observational studies, such as that in Muyinga. In practice, this distinction is frequently ignored. For more discussion, refer to: Direct and Indirect Effects in Vaccine Efficacy and Effectiveness, Halloran ME, *et al.*]

QUESTION 14A:
Using information on 12- to 23-month-olds in Muyinga provided in Table 13, estimate vaccine efficacy by the "screening method."

ANSWER 14A:
The nomogram provides a quick way of checking VE if PPV and PCV data are available via routine surveillance. If the VE thus obtained was substantially below that expected, then a special study to examine VE would be warranted.

This method is particularly useful when denominators and/or numerators are lacking to compute ARU and ARV, required for calculation of VE with the formula (ARU - ARV) / ARU.

Again because of excellent surveillance in Muyinga, age-specific PPV and PCV were available. The VE can be "eye-balled" from the nomogram or calculated precisely using this equation (represented by each curve on thenomogram):

$$VE = (PPV - PCV) / PPV (1-PCV)$$

Table 13. Vaccine coverage (PPV) and proportion of cases vaccinated (PCV), 12-23 months old, Muyinga

YEAR	PPV	PCV	VE (FROM NOMOGRAM)
1985	48%	6%	93%
1986	71%	17%	92%
1987	76%	41%	78%
1988	70%	31%	81%

These results suggest that a drop in VE may have occurred between 1985-1986 and 1987-1988. A special study (the census) was therefore organized to examine the VE, the results of which confirmed that the VE was within expected limits.

One possible explanation for the apparent drop in VE using the "screening method" is that the new surveillance forms capturing the vaccination status of cases were introduced in Muyinga in 1985. Health workers may not have adapted to capturing this information on a routine basis until 1987 through 1988. This would have resulted in falsely low PCV for 1985 and 1986, resulting in a falsely high VE.

A caveat therefore in interpreting the VE derived from the nomogram: "Garbage in, garbage out!" The VE obtained is only as reliable as the quality of the PPV and PCV data used. Overestimating coverage (PPV) results in overestimating VE. Underestimating PCV results in overestimating VE. Ideally, stable trends over years can be followed for any major deviations but it is risky to interpret data based on a new surveillance system. Another caveat about the nomogram, it is more "discerning" when the data is in the middle of the curve vs. at the ends of curve.

QUESTION 14B:
Compare these estimates with the vaccine efficacy obtained in Question 13.

ANSWER 14B:
Not too bad! The estimate from the nomogram seems to come closer to the calculated VE as the surveillance improves over time. While biased estimates from Tables 12A-12C tended to underestimate VE (misclassification bias), the most likely biases based on the nomogram (i.e., overestimating coverage and underestimating PCV) resulted in overestimating VE.

Instructor's Guide

Part IV
Measles Control Strategies

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

PART IV - MEASLES CONTROL STRATEGIES

[NOTE: *Answers 15-18* are identical to *Part V - Conclusions* of the exercise].

QUESTION 15:

Based on the data presented in Tables 14-16, what target age-groups would you recommend for measles vaccination in Burundi?

ANSWER 15:

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 may 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 can also be lowered to 6 months of age if a new more potent measles vaccine becomes available. This will further reduce the gap of susceptibility between maternal and vaccine-derived immunity.

QUESTION 16:

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

ANSWER 16:

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 inter-epidemic 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 occurred in 1989-1990 after 10 years of very low incidence and vaccine coverage among 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, or 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!!

QUESTION 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.

ANSWER 17:
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 campaigns, and 3) school-based programs.

c) vaccinate vaccine failures via a routine second dose. Note that the second dose should be called *revaccination* rather than *booster dose*, since the intent is to induce seroconversion in children with vaccine failure after the first dose, rather than to induce a boosting effect.

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 reduction in disease incidence rather than necessarily on acute outbreak control. 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 children.

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.

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

ANSWER 18:
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, or administration before target age). An investigation is 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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EXERCISES

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Part I

Vaccination Coverage

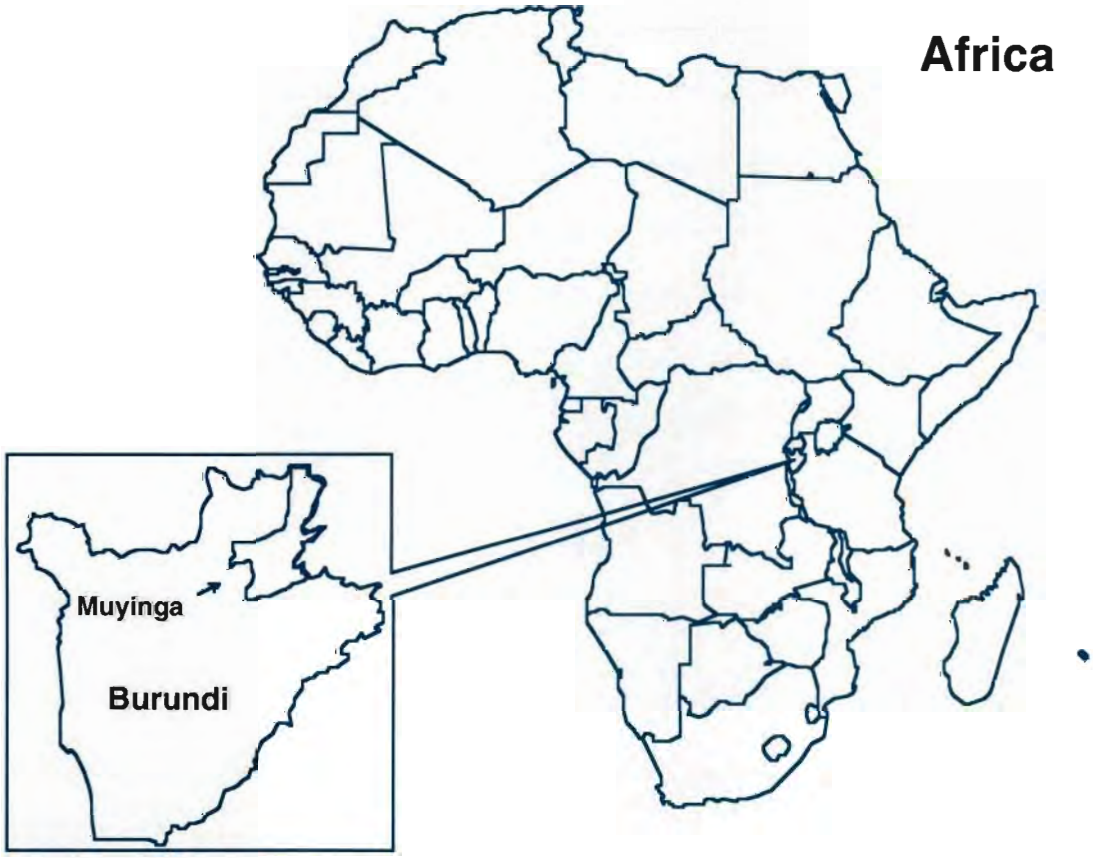
A Measles Outbreak in a Highly Vaccinated Population: Health Sector Muyinga, Burundi, 1988-1989

PART I - VACCINATION COVERAGE

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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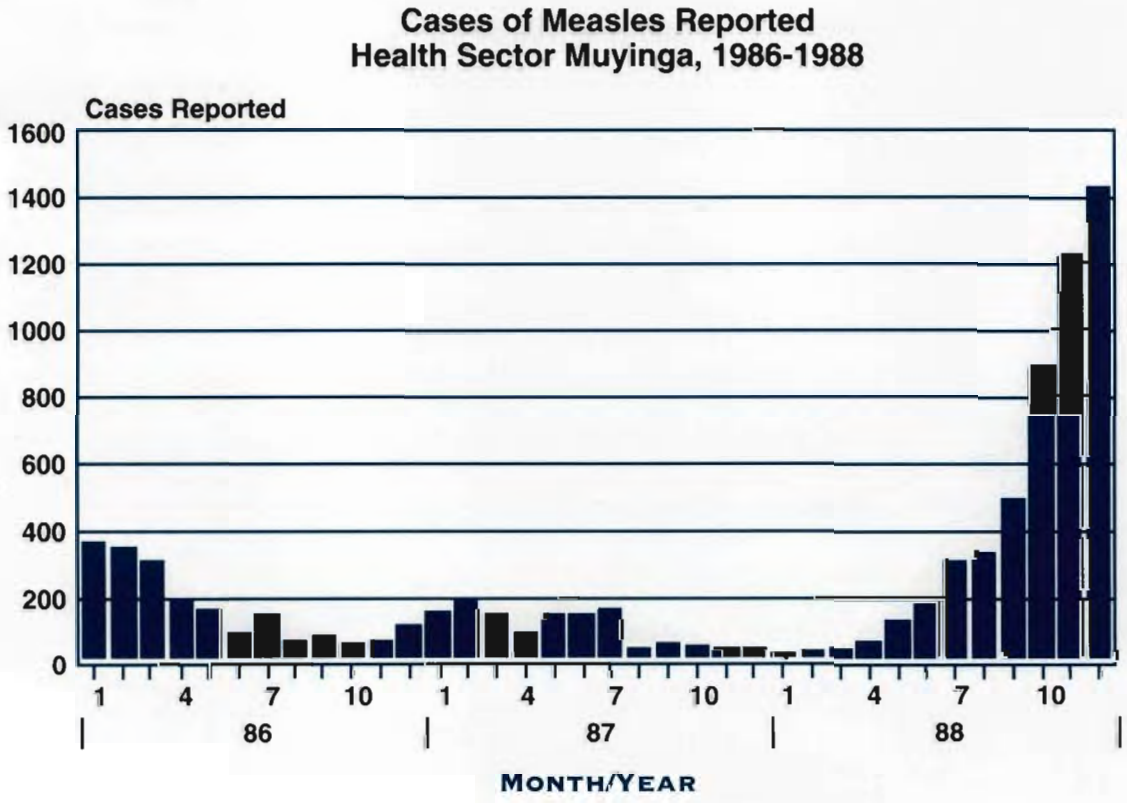
Burundi is a small densely populated nation located in east-central Africa, divided into 24 health sectors. Vaccination against measles, targeted at children 9 months of age, was introduced in 1981 in Burundi as part of the World Health Organization's (WHO) Expanded Programme on Immunization (EPI); children up to 2 years of age were also eligible. 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 1).

FIGURE 1



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?

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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 vaccination coverage of children up to 1 year of age for any vaccine (in this case, measles vaccine) can be estimated by taking the number of doses received by infants surviving until 1 year of age, divided by the number of such "surviving infants". By convention, the number of surviving infants is calculated as 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 2:

Assuming a crude birth rate of 4.8% and an infant mortality rate of 10.5%, calculate the number of infants born in 1987 in Burundi who survived to 1 year of age 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

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 in Burundi submit a Monthly Vaccination Report on doses of vaccines administered to each of two age groups: 0-11 months and 12-23 months. The eligible 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. The measles vaccine coverage for infants who reached 1 year of age in year Y was estimated by the equation:

$$\frac{\text{Doses 9-11 mo. year Y}}{\text{Surviving Infants Born in year (Y-1)}}$$

The above "administrative estimate" of vaccine coverage by 1 year of age is commonly used as a standard means to compare the performance of immunization programs in different regions or countries.

In this outbreak, because doses-administered data were also available for 12- to 23-month-olds and because an estimate of residual unvaccinated susceptible children in each birth cohort was needed, measles vaccine coverage by age 2 years was also estimated. Strictly speaking, the number of doses received by children before the age of 24 months is the sum of the number of

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dosesadministered to children ages 12-23 months during year (Y) plus the number of doses administered to children ages 9-11 months during the previous year (Y-1). Because the mortality rate of children 12-23 months of age was not readily available and was believed to be relatively small, the denominator was not adjusted for survival up to age 24 months. Thus, the estimated coverage for children who reached age 2 years during year Y was calculated as follows:

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

QUESTION 3:

Estimate the measles vaccination coverage in Burundi in 1988, and in Health Sector Muyinga in 1984 and 1988.

Table 3. Measles vaccination coverage, Burundi

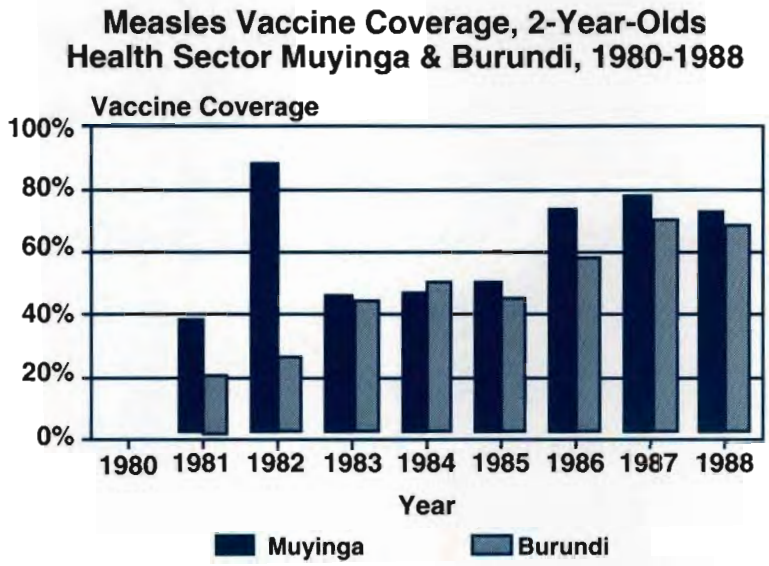
Year	Doses administered 9-11 mo (Y-1)	Doses administered 12-23 mo (Y) + 9-11 mo (Y-1)	Surviving infants born year(Y-1)	Coverage by Age 1	Coverage by Age 2
1984	52,539	90,020	189,024	28%	48%
1986	84,664	110,436	201,912	42%	55%
1988	145,528	138,140	210,504		

Table 4. Measles vaccination coverage, Health Sector Muyinga

Year	Doses administered 9-11 mo (Y-1)	Doses administered 12-23 mo (Y) + 9-11 mo (Y-1)	Surviving infants born year(Y-1)	Coverage by Age 1	Coverage by Age 2
1984	4,206	5,430	12,330		
1988	7,142	9,450	13,833		

Figure 2 shows the measles vaccination coverage by age 2 years 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 2



COVERAGE SURVEYS: Surveys using simple random sampling are rarely feasible in developing countries, since they require a complete enumeration of individuals 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 method was developed to obtain representative samples when a complete enumeration of children is not possible. The first-stage sampling involves the selection of 30 villages or neighborhoods, 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%

QUESTION 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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- NOTES -

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Part II

Disease Surveillance

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

PART II - Disease 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 3 and 4 summarize the 1980-1988 measles incidence and mortality data available to the EPI office, as well as the chickenpox incidence rate reported via the same surveillance system.

Figure 3

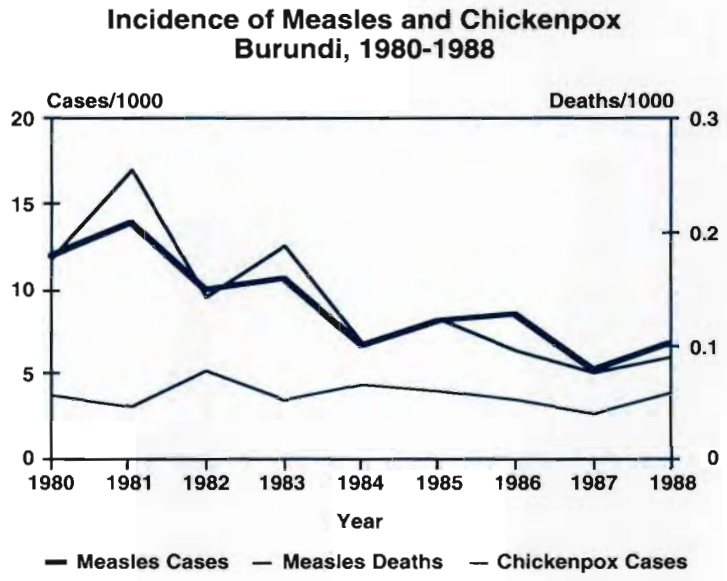
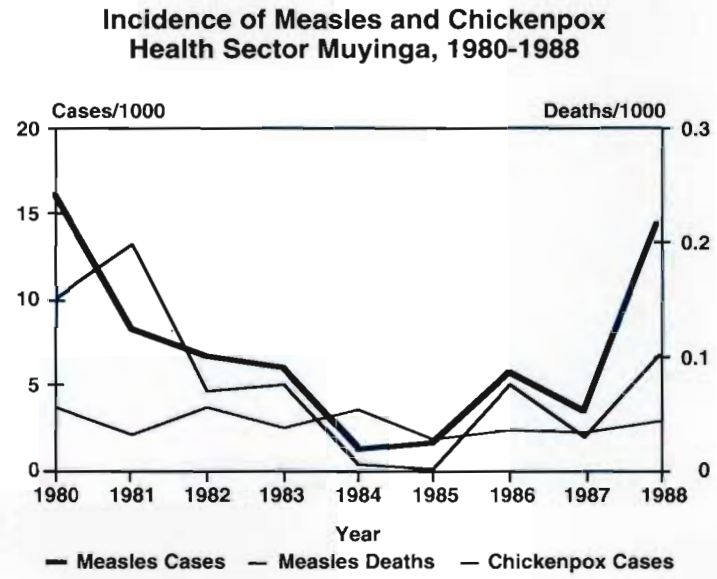


Figure 4



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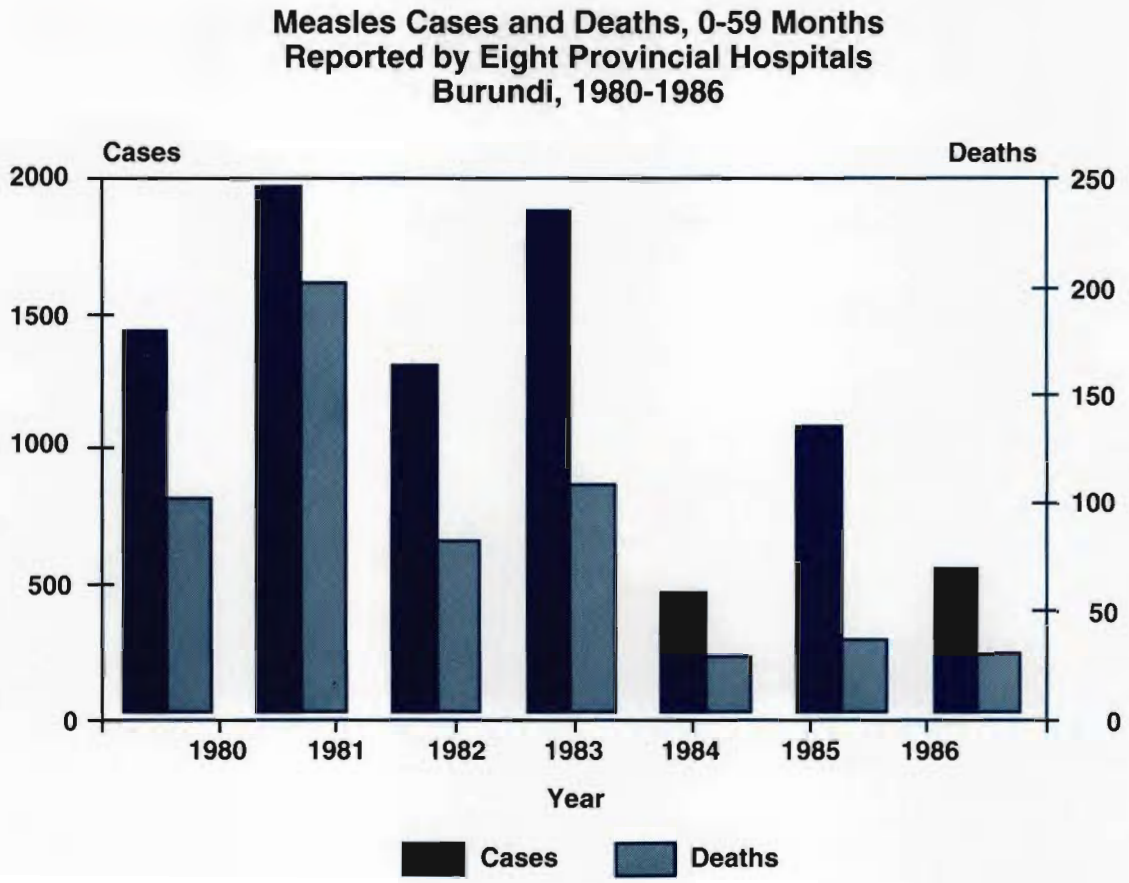
A recently completed study based on the registries of the eight major provincial hospitals provided additional data on persons admitted to hospitals for measles and deaths from measles, summarized in Figure 5.

FIGURE 5



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

QUESTION 6:
Use data on chickenpox incidence in Figures 3-4 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?

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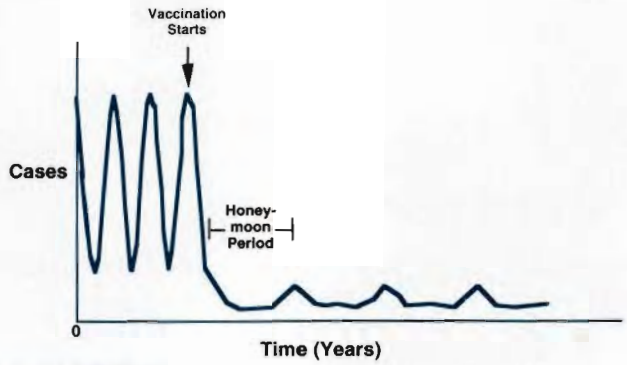
Figure 6 represents the epidemic cycle of measles in a rural region before and after the introduction of measles vaccination.

FIGURE 6



QUESTION 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 6). 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 Percentage of 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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- NOTES -

Part II Optional

Disease Surveillance

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

PART II - OPTIONAL- Disease Surveillance

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 7 and 8 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 7 and 8, calculate measles incidence, measles mortality, and chickenpox incidence rates for Burundi and Muyinga, 1980-1988. Figures for 1980 are given as example.

Table 7: Total Population, Measles and Chickenpox Cases, and Measles Deaths, Burundi, 1980-1988.

Year	1980	1981	1982	1983	1984	1985	1986	1987	1988
Population x 1000	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 8: Total Population, Measles and Chickenpox Cases and Measles Deaths, Health Sector Muyinga, 1980-1988.

Year	1980	1981	1982	1983	1984	1985	1986	1987	1988
Population x 1000	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								
Chickenpox Cases/1000	3.81								

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QUESTION 5B

Draw the corresponding graphs (Figures 3-4).

FIGURE 4

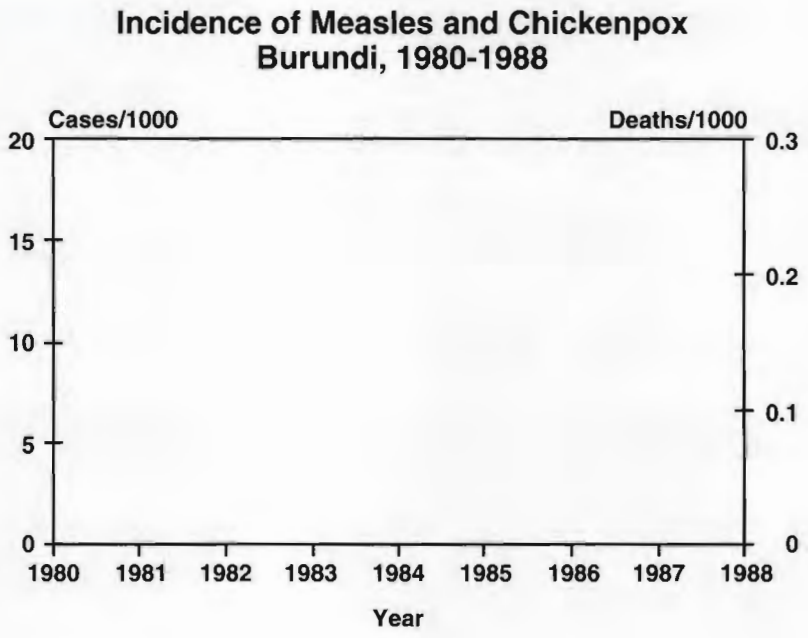
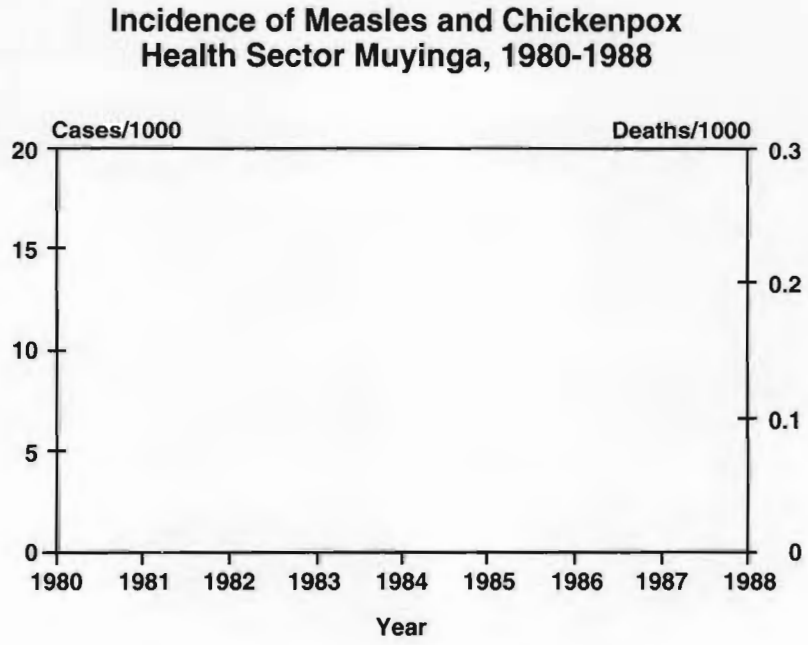


FIGURE 5



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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 9.

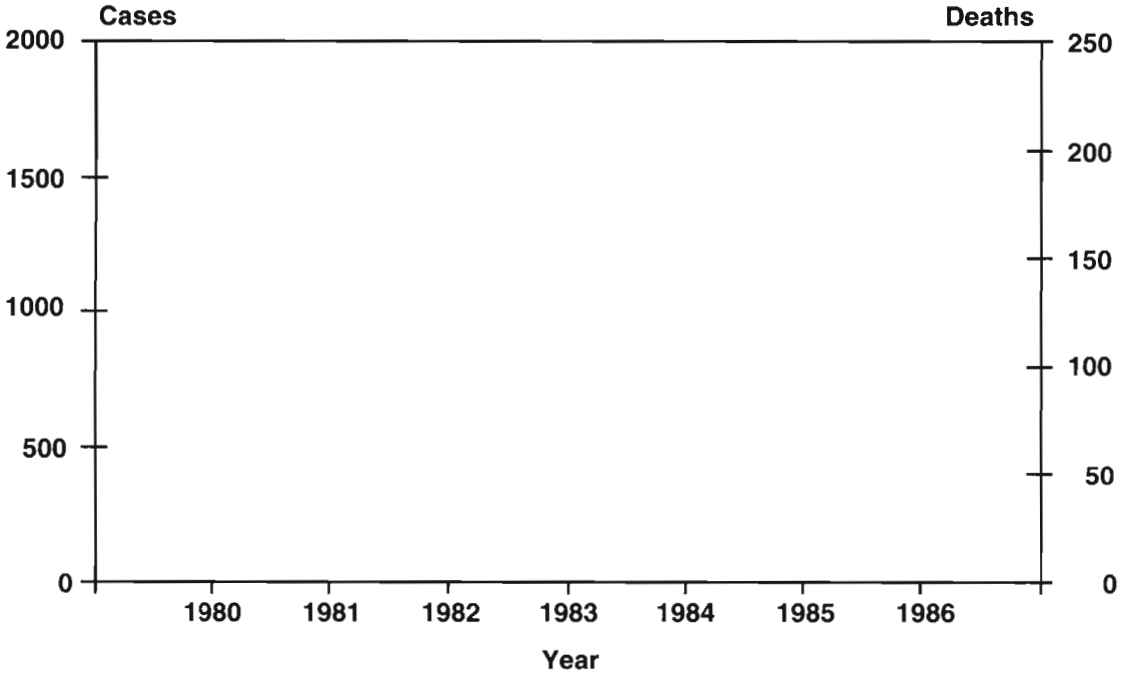
Table 9: Measles Cases and Measles Deaths, 0-59 months, 8 Selected Hospitals, Burundi, 1980-1986.

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 5) the data on measles cases and measles deaths in hospitals presented in Table 9.

FIGURE 5

Measles Cases and Deaths, 0-59 Months
Reported by Eight Provincial Hospitals
Burundi, 1980-1986



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QUESTION 5D

Using Figures 3-5, describe and interpret the trends in measles morbidity and mortality in Burundi and Health Sector Muyinga.

QUESTION 6:

Use data on chickenpox incidence in Figures 3-5 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?

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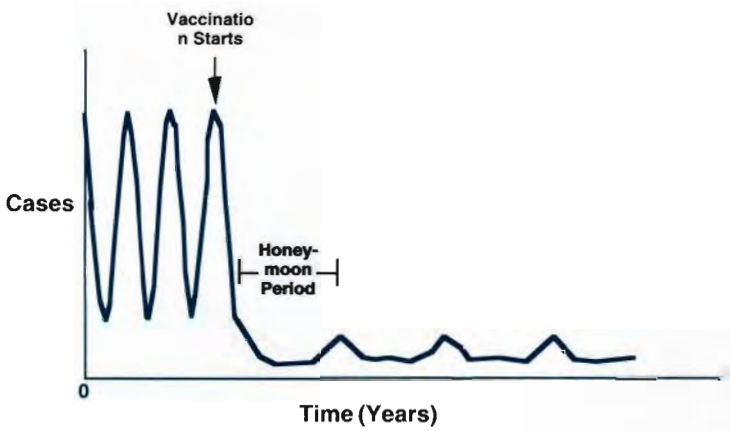
Figure 7 represents the epidemic cycle of measles in a rural region before and after the introduction of measles vaccination.

FIGURE 6



QUESTION 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 6). Can you explain why?

In Health Sector 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 Percentage 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%

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QUESTION 10A:
Using data from Table 6, represent graphically the percentage distribution of measles cases (Figure 7) and the measles cases by age group (Figure 8).

QUESTION 10B:
Using Figures 7-8, describe and interpret the changes in the age distribution of measles cases in Health Sector Muyinga.

FIGURE 7

Percentage Age Distribution of Measles Cases
Health Sector Muyinga, 1985-1988

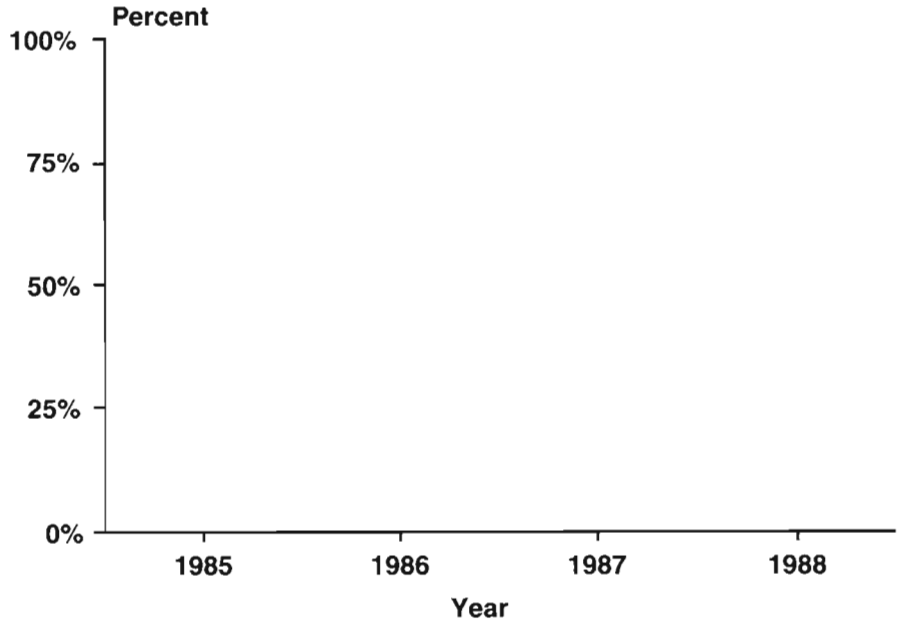
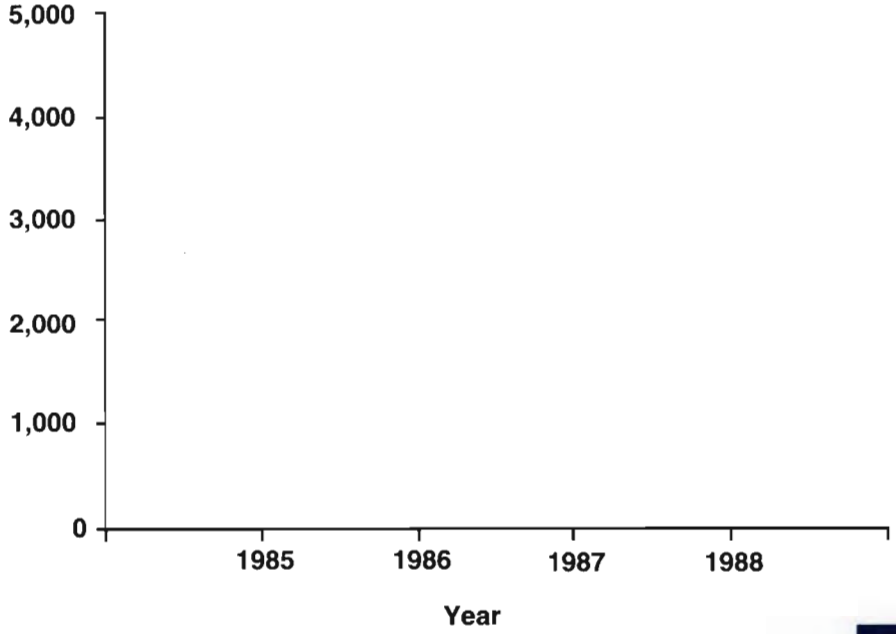


FIGURE 8

Meales Cases, by Age Group
Muyinga, 1985-1988



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Part III

Vaccine Efficacy

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

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 10. Vaccination status of measles cases, Health Sector Muyinga

Year	Number of measles cases	Proporition 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?

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Table 11 provides data for calculating the Percentage of 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 11. Hypothetical populations with vaccine coverage of 20%, 60%, and 100%

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

QUESTION 12:

Complete Table 11. What can 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. 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 of age 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 12A-12D):

QUESTION 13:

Using the equation provided above, calculate the vaccine efficacy for Tables 12B-12D (calculations for Table 12A are given as an example). Discuss the reasons for the differing results obtained.

Table12A. All children in census (measles cases as reported by mother; children without vaccination card counted as unvaccinated)

	MEASLES	NO MEASLES	TOTAL
VACCINATED	115	893	1,008
UNVACCINATED	207	685	892
TOTAL	322	1,578	1,900

ARU = 207/892 = 23% **ARV** = 115/1,008 = 11%

VE = (23% - 11%) / 23% = 1 - (11% / 23%) = 51%

Table 12B. Unvaccinated children restricted to those with vaccination cards (on which there is no record of measles vaccination).

	MEASLES	NO MEASLES	TOTAL
VACCINATED	115	893	1,008
UNVACCINATED	122	316	438
TOTAL	237	1,209	1,446

ARU = _____ **ARV** = _____ **VE** = _____

Table 12C. Criteria in 12B 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	50	893	943
UNVACCINATED	60	316	376
TOTAL	110	1,209	1,319

ARU = _____ **ARV** = _____ **VE** = _____

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Table 12D. Criteria in 12B and 12C and analysis restricted to children ≥9 months of age

	MEASLES	NO MEASLES	TOTAL
VACCINATED	41	701	742
UNVACCINATED	31	118	149
TOTAL	72	819	891

ARU = _____ ARV = _____ VE = _____

The attached nomogram (Figure 9, 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 13, estimate vaccine efficacy by the "screening method" (estimate of Vaccine Efficacy for 1985 is given as example).

Table 13. Vaccine coverage (PPV) and proportion of cases vaccinated (PCV), 12- to 23-month-olds, Muyinga

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 vaccine efficacy obtained in Question 13.

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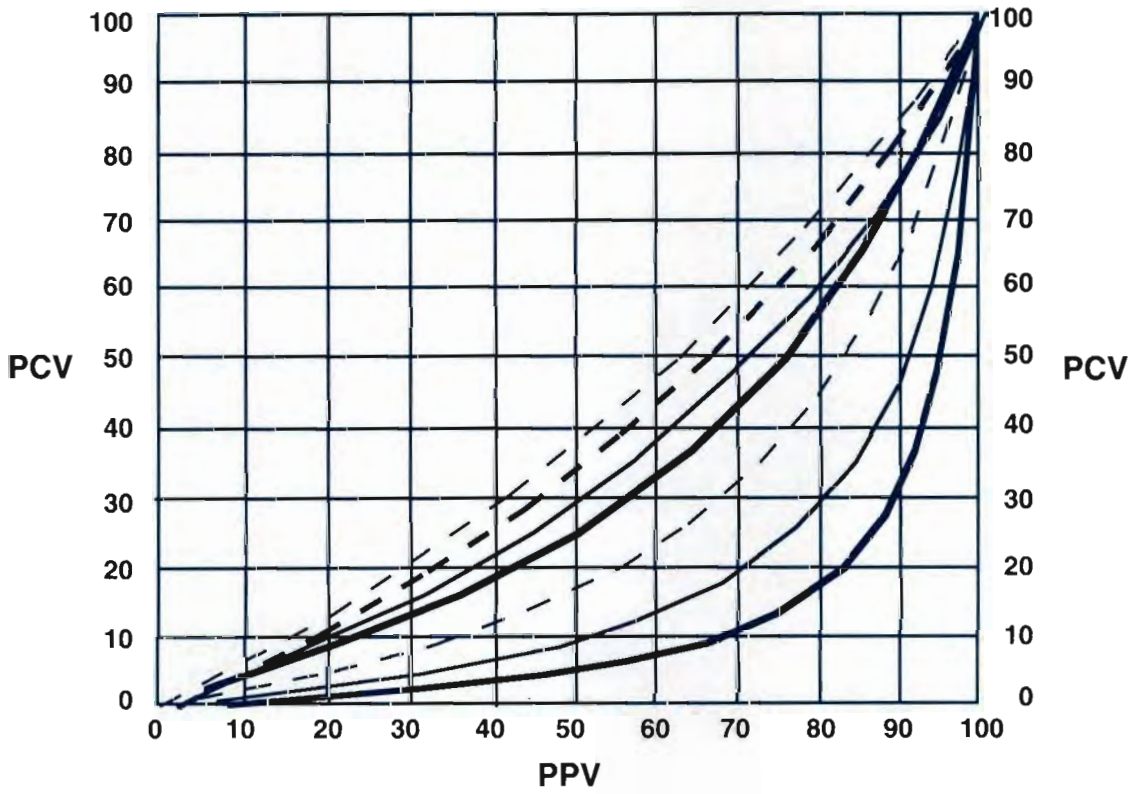
NOMOGRAM: Percentage of cases vaccinated (PCV) per percentage of population vaccinated (PPV), for seven values of vaccine efficacy (VE).

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

FIGURE 8



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

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

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Part IV

Measles Control Strategies

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

PART IV- MEASLES CONTROL STRATEGIES

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 14. Measles attack rate by age group, Health Sector Muyinga census

Age group (months)	Census	Measles cases	Attack rate	% of total
0-5	206	18	9%	6
6-8	142	45	32%	15
9-23	522	124	24%	42
24-59	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

	Ill with measles			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:

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Table 16. Measles cases, Cumba Primary School, Health Sector Muyinga 1988

GRADE	ENROLLMENT	MEASLES CASES	ATTACK RATE	INDEX 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%

* Index cases = Measles cases in children who were the first persons with measles in their households. These 25 index cases were followed by a total of 31 secondary household cases, 28 (90%) of which were among younger siblings.

QUESTION 15:

Based on the data presented in Tables 14-16, what target age-groups would you recommend for measles vaccination in Burundi?

QUESTION 16:

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

QUESTION 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?

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Part V

Conclusions

A MEASLES OUTBREAK IN A HIGHLY VACCINATED POPULATION: HEALTH SECTOR MUYINGA, BURUNDI, 1988-1989

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 can also be lowered to 6 months of age if a new more potent measles vaccine 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 occurred in 1989-1990 after 10 years of very low incidence and vaccine coverage among 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 campaigns, and 3) school-based programs.

c) vaccinate vaccine failures via a routine second dose.

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 reduction in disease incidence rather than necessarily on acute outbreak control. 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

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