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Sample design and procedures for Hepatitis B immunization surveys: A companion to the WHO cluster survey reference manual

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Contents

I. Introduction

This document is designed to supplement the sample design, sample selection and sample size determination guidance report provided by the World Health Organization (WHO), "Immunization Cluster Survey Reference Manual" (WHO, 2005). All information is presented with a focus on sero-prevalence surveys that are used to assess Hepatitis B vaccination program impact as well as surveys that are used to assess Hepatitis B vaccination program performance. In particular, we will emphasize how to measure low prevalence population characteristics, such as Hepatitis B surface antigen (HBsAg) in countries with low Hepatitis B endemicity (<2% HBsAg).

Hepatitis B vaccine programs have been widely implemented over the past decades and were able to decrease the percentage of chronic Hepatitis B infections and liver cancer among children (Chang et al. 1997, Mast et al. 2004, see table 1.1). In fact, two regional offices of the WHO have declared prevalence targets of chronic Hepatitis B virus infections. The Western Pacific Regional Office (WPRO) declared in 2007 to reduce chronic hepatitis B infection in children aged at least five years to <2% by 2012 as an interim milestone towards the final goal of <1% (WPRO 2005). The Eastern Mediterranean Regional Office (EMRO) aims at a reduction of chronic Hepatitis B virus infections to less than 1% among children less than 5 years of age by 2015. The WPRO has even established a certification procedure to document national achievement of Hepatitis B control (WPRO 2007). One of the requirements for certification is that at least one representative serosurvey measuring the HBsAg rate in the selected population (e.g. birth cohorts after the introduction of a national Hepatitis B vaccination program) is conducted. This document is written as an aid to researchers and health professionals who are preparing to conduct such a Hepatitis B vaccination program impact assessment or HBsAg sero-prevalence survey.

The emphasis of this report lies on using probability sampling methods for population surveys; however, we wish to acknowledge at the outset that a population survey is not the only tool and in some cases not the best tool for measuring the effectiveness of a vaccination program. Depending on the specific objectives of the study, assessments based on administrative systems or procedures involving monitoring by medical clinics and public health agencies may be more cost effective and less labor intensive than one-time population surveys. Examples are studies by Mele et al. (2008) and Madani (2007) who used population-based surveillance systems to measure the incidence of acute Hepatitis B infections. It should also be noted that specific considerations have to be made when a conventional population survey is used to assess extremely low prevalence conditions (<1-2%) because it is likely that nonsampling errors may bias the final prevalence estimate. This report will introduce readers to the concepts of nonsampling errors and guide them in adjusting their sample design to minimize biases introduced in the final prevalence estimate.

It should generally be noted that although the focus of this report is on Hepatitis B immunization coverage and sero-prevalence surveys, the methods described can also be applied to other immunization surveys or epidemiological studies of rare population characteristics.

1.A Background

Why do surveys of rare population characteristics or events require special sample designs or survey procedures? First, conventional sample designs and traditional survey methods that work very well in a general, multi-purpose study may not be efficient for a survey of rare events and conditions. Second, the relative importance of sampling bias and nonsampling errors to the total survey error of the data is much greater when the outcomes of interest are not common in the target population of the survey. Finally, traditional survey procedures may not be cost effective for surveys of rare events and conditions.

Historically, the WHO's Expanded Programme on Immunization (EPI) cluster survey method (Henderson and Sundaresan, 1982) was developed to be low cost and practicable and to deliver useful but not highly precise estimates of vaccination rates in target populations. The original EPI cluster survey method certainly proved practical and popular. In a 1994 paper, Brogan et al. cite a total of 4502 documented uses of the survey method reported to the WHO. The EPI cluster survey method or simple modifications of the basic method have been important tools in rapid assessments of progress in the worldwide efforts in vaccinating children and adults against infectious diseases. As progress in immunization coverage for target populations has been achieved, epidemiologists and health planners are conducting assessments of immunization programs that are much more statistically demanding than the quick coverage surveys conducted under the EPI cluster survey method.

Part of the challenge in the design of contemporary surveys to evaluate Hepatitis B vaccination programs can be attributed to the very effectiveness of these programs in achieving vaccination coverage in infants and reducing the levels of chronic infection in children and the population at large. Table 1.1 is an excerpt from Mast et al. (2004) that illustrates this point.

Table 1.1: Effectiveness of HepB vaccination in reducing the prevalence of chronic HBV infection (HBsAg positive) (Mast et al., 2004)

Study Site	Follow-up Years	HepB3 coverage achieved %	% chronic infection, before HepB vaccination	% chronic infection, after HepB vaccination
Alaska[1]	1-10	96	16	0.0
Gambia[2]	9	100	10	0.6
Italy[3]	6-14	95	6.8	0.7
Taiwan[4]	6	92	10.5	1.7

[1] Harpaz et al. (2000), [2] Viviani et al. (1999), [3] DaVilla et al. (1998), [4] Hsu et al. (1999)

Prior to the introduction of the HepB vaccination program, 16% of the Alaskan population studied by Harpaz et al. (2000) had a chronic HBV infection. Based on follow-ups conducted one to ten years following the program introduction, chronic infections had virtually disappeared from the study population. Chronic infection rates in the Taiwanese population studied by Hsu et al. (1999) went from 10.5% in the pre-program years to 1.7% by six years following the start of a mass vaccination effort.

Chronic infections in as few as 1-2% of the population constitute a rare event. Likewise, a child that is not vaccinated in a population where vaccination coverage exceeds 97% is "rare". The terms, "rare event" or "rare condition", do not have formal statistical definitions. In this document, these terms will be used to refer to events (e.g. a new viral infection) or conditions (e.g. presence of antibodies) affecting from <1% to 10% of the survey population.

1.B Distinguishing surveys of rare characteristics and surveys of rare populations

The focus of the discussion in this document is on surveys designed to estimate the prevalence of rare characteristics in a population. The reader should note that the primary objective underlying the methods in this document is not to screen for rare elements in the population for purposes of an in-depth study. Kalton (1992) carefully distinguishes between surveys to estimate the prevalence of rare characteristics and those designed to sample and study the rare population elements. An example is useful to make the distinction between these two types of survey design problems:

Example 1.1:

A public health officer is interested in estimating the prevalence of unvaccinated children in a local health district. The district has a mature HepB infant vaccination program and the expected vaccination noncoverage rate for children under 10 is 5%. The officer's sampling consultant informs her that she will need a probability sample of 475 children to estimate the noncoverage rate with a 95% confidence interval of +/- 2%.

An epidemiologist in the same health district is interested in studying unvaccinated children—specifically to estimate the proportion of those children who received only 1 of the 3 doses in the HepB vaccination sequence. The sampling statistician informs him that if the percentage of unvaccinated children who received the 1st inoculation among all unvaccinated children is 40% he will need a sample of 2400 unvaccinated children to ensure a 95% confidence interval (CI) of +/- 2%. However, since roughly