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EXPANDED
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Protocol for assessing
prevalence of Hepatitis B infection
in antenatal patients



WORLD
HEALTH
ORGANIZATION

PROTOCOL FOR ASSESSING PREVALENCE OF
HEPATITIS B INFECTION IN ANTENATAL PATIENTS

1. BACKGROUND

Hepatitis B virus (HBV) infection is a disease of major public health importance worldwide, as a cause of both acute hepatitis and of chronic liver disease (chronic active hepatitis, cirrhosis, and primary hepatocellular carcinoma) due to persistent viral infection. Worldwide patterns of disease transmission vary widely from a highly endemic disease transmitted primarily at birth (perinatally) or in childhood (east and southeast Asia and sub-Saharan Africa), to a low endemicity disease transmitted primarily by blood and by sexual contact among adults (western Europe and North America).

Strategies for use of HB vaccine in different parts of the world will differ according to endemicity of disease. In areas of high HBV endemicity (>8% HBV carriers), prevention of perinatal and early childhood transmission is of highest importance, and universal immunization of infants, starting at birth, has been advocated.

Health planners worldwide are trying to determine what priority should be given to HB immunization in their country, and what strategy for vaccine delivery should be adopted. The availability of valid data and the ability to interpret it correctly are important in making this decision.

1.1. Data from serological studies

Valid data may come from serological studies done in the country or in nearby countries with similar populations. Hepatitis B prevalence differs markedly between North America and Africa, for example, but varies little between the countries of sub-Saharan Africa. All countries in sub-Saharan Africa and Asia east of Myanmar (Burma) have hyperendemic levels of HBV transmission. It would make sense for all these countries to integrate HB vaccine into their EPI. Additional serological surveys to prove this point one more time are unnecessary; lack of survey data within a country should not be used as an excuse for inactivity.

There are several reasons why serological surveys may be considered:

- Data from one's own country may be more convincing to policy-making health officials.

- Countries with diverse ethnic groups may have markedly different HBV prevalence in some of the groups. For example, Singapore has significant differences between the Indian, Chinese and Malay populations.
- Knowing the prevalence in pregnant women of HBsAg and HbeAg will reveal the relative importance of mother-to-child transmission in the population. This information may be useful in deciding whether the first dose of HB vaccine is administered at birth or with DPT-1.

There are some problems with accepting data from earlier studies. Existing data must be examined critically. Laboratory tests for HBV markers have evolved and "third generation" tests of high sensitivity and specificity are now available. Older data using less sensitive tests are not necessarily invalid, but may underestimate true marker prevalence.

A more important source of bias is studies that measure serological markers in convenient but unrepresentative groups such as professional blood donors, prisoners, or hospital inmates such as dialysis or cancer patients. Sometimes studies also ignore basic epidemiological techniques such as age standardization.

1.2. Sampling blood donors

Many countries will want to examine the HBsAg prevalence in their blood donor population, since results of such testing may be available. HBsAg positive individuals identified in this manner are almost always chronic HBV carriers, and if volunteer (not professional or paid) blood donors are recruited from a wide geographical area, the prevalence of HBV carriage in the blood donor population may be a crude indicator of the carrier prevalence in the general population. However the rate in blood donors often under-estimates the true prevalence in the population for several reasons:

- healthy volunteers are more likely to be accepted as donors,
- donors are not accepted if they give a history of hepatitis or liver disease,
- donors may not be representative of the population in respect to socio-economic status or ethnicity,
- donors found on screening to be HBsAg positive will not be asked to donate again. Thus repeat donors are less likely to be HBsAg positive. Therefore, if blood donor prevalence is being measured, it is important to measure the prevalence in first-time donors.

1.3. Other sources of data

Other types of data may be very useful to health officials for planning, and for educating health care providers and the public about the risks of HBV infection. Such data include:

- an estimate of the relative importance of liver cancer, obtaining data from cancer registries or records of pathology. Liver cancer is usually the first or second cause of cancer death in males where HBV infection is hyper-endemic.

- data from hospital discharges of acute hepatitis, chronic hepatitis, cirrhosis and liver cancer. Other diagnoses such as "jaundice", "ascites" and "oesophageal bleeding" also conceal hepatitis-related pathology.

While it is important to obtain accurate information on the prevalence of hepatitis B, the difference of a few percentage points in the prevalence of antigen markers between different population groups may not be of great importance from a public health perspective. In hyper-endemic areas, a decision must be taken whether to immunize all newborns or none. It is unlikely that a decision to provide selective immunization would be chosen in developing countries where such a policy would have little or no value.

2. BASIC APPROACH TO EPIDEMIOLOGICAL STUDIES

2.1. Types of surveys

Currently the most relevant epidemiological approaches include:

- assessing the importance of perinatal HBV transmission;
- assessing the importance of HBV transmission in early childhood.

Disease transmission in early childhood is extremely important in high HBV endemicity areas and often important in moderate HBV endemicity areas. Cross sectional surveys of the general population of young adults are important to assess uniformity of risk among different segments of the population.

2.2. Components of survey

Systematic surveys to assess HBV prevalence should include:

- administration of a questionnaire to each person to define demography and possible epidemiological risk factors for HBV infection and,
- obtaining a blood specimen for testing for hepatitis B markers.

Critical features to assess by questionnaire (see appendix 1) include:

- age,
- sex,
- racial group (specifically as defined within the country),
- geographical location of residence (city or town, urban or rural);

To define the prevalence of HBV infection, serum specimens should be tested for the presence of markers of active infection (HBsAg) or past HBV infection (anti-HBs or anti-HBc). The former assesses risk of active infection, and identifies those at risk of chronic disease and transmission to others. The latter assess the overall prevalence of prior HBV infection, which is usually five to twenty times higher than the prevalence of HBsAg positivity. Because of this, the antibody tests are much more efficient for accurately estimating disease frequency in a population.

When studies are being conducted to determine the role of perinatal transmission of HBV in the country's disease burden, HBsAg positive samples from pregnant women should also be tested for HBeAg and anti-HBe. This marker (HBeAg) is the best predictor of the likelihood of HBV transmission from mother to infant. Radioimmunoassays (RIA) or Enzyme Immunoassays (EIA) should be used, as only these tests have adequate sensitivity.

Certain cautions must be advised when using these tests: the commercially available EIA tests for HBsAg and anti-HBc have somewhat lower specificity than the corresponding RIA assays, and ideally all positive results (or at least those for HBsAg) should be retested or confirmed with neutralization. The anti-HBs EIA has excellent specificity and does not require confirmation.

2.3. Analysis of results and samples sizes

In general, the prevalences of HBsAg positivity and of all prior HBV infections (positivity for HBsAg or anti-HBs or HBc) should be estimated for the group studied as a whole, and then related to various factors which may affect HBV infection in the population (demographic factors and epidemiological exposures).

Sample sizes for these studies should ideally be large enough to define in general terms HBV endemicity in the population studied and to discriminate risk according to relevant factors. The broad endemicity patterns as defined in adults include:

low prevalence (less than 1% positive for HBsAg and/or less than 15% with prior infection);

moderate (2-7% prevalence of HBsAg and/or 15-40% with prior infection);

high (> 8% HBsAg and/or > 45% with prior infection).

Since the prevalence of HBsAg may be low (less than 10%), the study of very large populations would be needed to differentiate small differences in endemicity. For example, to demonstrate low (1%) vs. moderate (4%) endemicity requires a group size of about 1200 (with 95% confidence interval).

In contrast, the prevalence of prior HBV infection is usually much higher (10-70%), but still accurately reflects risk of HBV infection; it therefore can be used to discriminate low (10%) vs. moderate (40%) endemicity of prior infection with 95% confidence in a much smaller samples (N = about 100). Therefore, by using overall HBV prevalence as the primary measure of disease risk, sample size may be roughly based upon a baseline of 100 for an homogeneous population, multiplied by the number of factors (racial, urban/geographic) expected to affect HBV infection prevalence. For large nationwide studies, statisticians should be consulted to assist in estimating sample size.

PROTOCOL FOR PREGNANT WOMEN

Pregnant women represent a convenient group to study in that they may be easily accessed in antenatal clinics or in hospitals. Relevant subgroup (i.e. low vs. high socio-economic status) can often be accessed in the same settings, and all subgroups may be assessed by proper selection of clinics or hospitals. In addition, studies in pregnant women may be used to estimate overall HBV prevalence in young adults, as these rates rarely vary by sex.

Specific purposes

- To define the prevalence of HBsAg positive women, and among these the number who are HBeAg positive, to determine the risk of perinatal HBV transmission in a population.
- To define the risk of prior HBV infection in a population of young adults to estimate the overall disease endemicity in the population.

Method

1. Study population - women attending antenatal clinics and/or giving birth in hospitals in one or more localities (cities, etc.); ideally study sites should be selected to broadly represent the population in the country.
2. Questionnaire - as defined in Appendix 1.
3. Serological testing - HBsAg and either anti-HBs or anti-HBc. For all HBsAg positive specimens, test for HBeAg/anti-HBe.
4. Sample size - The sample size necessary to estimate accurately an HBsAg prevalence of 1-4% and to generate enough HBsAg positive samples for estimating HBeAg prevalence will be about 500. This will also be adequate to define overall prevalence of HBV infection and to define higher risk segments of the population in the study area.

5. Data Analysis

- a) Calculate the prevalence of HBsAg and of HBeAg in the study population. The frequency of HBsAg/HBeAg positive women gives the best measure of the risk of perinatal HBV transmission. Because most infants infected at birth remain lifetime HBV carriers, one can crudely estimate the contribution of perinatal transmission to the overall HBV carrier rate. (See Appendix 2).

If the HBsAg prevalence is high, HBsAg prevalence by age or by other risk factors may be calculated.

- b) Calculate overall prevalence of HBV infection in young adult women. This can be used to interpret the likely disease transmission patterns in the population (see Table 1).

6. Conclusions

The results of studies in pregnant women may be used to develop policies for prevention of HBV transmission and to define needs for other studies in the population. If studies show a moderate to high disease endemicity, then studies of young children will be necessary to define the relative importances of perinatal vs. childhood transmission and programmes of infant immunization will be necessary.

If studies show a low HBV endemicity among young women as a whole and in specific risk groups, then other studies such as HBV prevalence in young children are not necessary, and perinatal prevention may focus on screening to identifying HBV carrier mothers during pregnancy and providing specific prophylaxis to their children. Further studies may also be necessary if certain segments of the population are found to have a moderate or high disease endemicity in a low endemicity population; specific or unique immunization strategies may be necessary for such groups. However, only universal immunization of newborns is likely to control hepatitis B in the long term.

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APPENDIX 1

SAMPLE QUESTIONNAIRE FOR EPIDEMIOLOGICAL STUDIES

Name: _____

Names of Parents (if child): (Father) _____

(Mother) _____

Age: _____

Sex: _____

Ethnic/racial group (European; African; Indigenous; Mixed; Asian; other):

Geographic:

Location of birth or longest childhood residence: _____

Type of location: City: Population > 500,000; 100,000-500,000;
10,000-100,000); Town/village: (1000-10,000; < 1000)

OPTIONAL: (depending on the needs of the survey)

Socio-economic/family income (in discrete categories): _____

Educational level (years schooling): (primary=1-6 years; Secondary=7-12 years;
University=13 or more years)

Self: (if adult) _____

Father: (if child) _____ Mother: (if child) _____

Hepatitis History _____

APPENDIX 2

EXAMPLES OF ESTIMATES OF PERINATAL AND CHILDHOOD DISEASE
TRANSMISSION FROM SEROPREVALENCE DATA

1. Estimates of frequency and importance of perinatal HBV transmission

Example: Rural Amazon Basin, Brazil - study involving women of childbearing age (reference 5).

HBsAg prevalence - 6.0%

HBV infection prevalence = 60%

HBeAg prevalence = 19% in HBsAg positive women

Prevalence of HBsAg and HBeAg positive mothers

$$= .06 \times .19 = .0114 = 1.14\%$$

Frequency HBV carriers in population due to perinatal infection

$$= .0114 \times .80 \text{ (efficiency of perinatal transmission)}$$

$$= .00912 = .91\%$$

Proportion HBV carriers due to perinatal infection

$$= .00912 / .06 = 15.2\%$$

Interpretation - High HBV endemic population, significant risk of perinatal disease transmission but likely that childhood transmission also important

2. Estimates of importance of HBV transmission in early childhood

Example: Rural Amazon Basin - study involving children age 5-9 years. (ref.5)

HBsAg prevalence - 10.4%

HBV infection prevalence = 49%

Estimated frequency of perinatal transmission (same study)

$$= 0.91\% \text{ (see Example 1. above)}$$

Ratio of childhood to perinatal infection in causing HBV carriage in children

= (HBsAg prevalence in children) minus (HBsAg prevalence due to perinatal infection) divided by (HBsAg prevalence due to perinatal infection).

$$= (10.4 - 0.91) : 0.91 = 10.5:1$$

Interpretation: High HBV endemicity, 50% children infected before age 10; childhood transmission is more important than perinatal transmission

TABLE I

Examples of studies in different countries showing varying levels of HBV markers and their significance.

Prevalence of HBV markers				Interpretation		
Area/group studied	HBsAg	HBeAg*	Prior HBV infection	Likely importance of transmission		
				Perinatal	Childhood	Adult
Chile, Argentina	< 1%	20%	5-15%	Moderate (accounts for 15% of HBV carriers)	Minimal	Moderate
Venezuela, NE Brazil	1-3%	20%	15-45%	Moderate (as above)	Moderate	Moderate
Africa	7-15%	15%	70-90%	Moderate (accounts for 10% of HBV carriers)	High	Low
Southeast Asia	7-15%	40%	70-90%	High (accounts for 30% of HBV carriers)	High	Low

* - % of HBsAg individuals who are also HBeAg positive

REFERENCES

1. Maynard J.E., Kane M., Hadler S.C. The Global Control of Hepatitis B Through Vaccination. Rev. Inf. Disease 1987 in press.
2. Centers for Disease Control. Recommendations for Protection Against Viral Hepatitis. MMWR 1985; 34:313-24, 329-35.
3. Fay O.H., Hadler S.C., Maynard J.E., Pinheiro F. Hepatitis in the Americas. Pan American Health Organization Bulletin 1985; 19:401-408.
4. Hadler S.C., Hepatitis in the Americas - Update. Presented at Second Meeting of the PAHO Advisory Group on Viral Hepatitis. Caracas, Venezuela. Sept. 1986.
5. Bensabath G., Hadler S.C., Pereira-Soares M.C., Fields H., Maynard J.E. Epidemiologic and Serologic Studies of Acute Viral Hepatitis in Brazil's Amazon Basin. PAHO Bulletin 1987; 21:16-26.
6. Pasquini P., Jahn H.A., Pileggi D., et al. Prevalence of Hepatitis B Marked in Italy. Am J. Epidemiol. 1983; 118:699-709.

