

## Chapter 4: Hepatitis B

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### I. Disease Description

Hepatitis B is caused by infection with the hepatitis B virus (HBV), a partially double-stranded DNA virus of the family hepadnaviridae. HBV replicates in the liver and causes both acute and chronic hepatitis. Although the highest concentrations of virus are found in blood, other body fluids, such as semen and saliva, have also been demonstrated to contain HBV.<sup>1</sup> HBV is predominantly a blood and sexually transmitted infection and is transmitted by percutaneous and mucosal exposure to infectious body fluids.

#### *Symptomatology and transmission*

The incubation period for acute hepatitis B ranges from 45 to 180 days (average 120 days). The clinical manifestations of acute HBV infection are age dependent. Infants, young children (younger than 10 years of age), and immunosuppressed adults with newly acquired HBV infection are usually asymptomatic.<sup>2</sup> Older children and adults are symptomatic in 30%–50% of infections. When present, clinical symptoms and signs might include anorexia, malaise, nausea, vomiting, abdominal pain, jaundice, dark urine, and clay-colored or light stools. Occasionally, extrahepatic manifestations occur and include skin rashes, arthralgia, and arthritis. Fulminant hepatitis occurs in about 1%–2% of acutely infected persons.

Among adults with normal immune status, most (94%–98%) recover completely from newly acquired HBV infections, eliminating the virus from the blood and producing neutralizing antibodies that confer immunity from future infection.<sup>3</sup> In infants, young children, and immunosuppressed persons, most newly acquired HBV infections result in chronic infection.<sup>4,5</sup> Infants are at greatest risk, with a 90% chance of developing chronic infection if infected at birth.<sup>6</sup> Although the consequences of acute hepatitis B can be severe, most of the serious sequelae occur in persons in whom chronic infection develops. Chronic liver disease develops in two-thirds of these persons, and approximately 15%–25% die prematurely from cirrhosis or liver cancer. Persons with chronic HBV infection are often detected in screening programs, such as those for blood donors, pregnant women, and refugees.<sup>1,7</sup> Persons with chronic HBV infection are a major reservoir for transmission of HBV infections. Any person testing positive for hepatitis B surface antigen (HBsAg) is potentially infectious to both household and sexual contacts.

### II. Background

#### *Prevalence*

Globally, there were an estimated 248 million persons with chronic HBV infection in 2010 and approximately 686,000 deaths were attributed to complications associated with chronic HBV infection in 2013.<sup>8</sup> In the United States, based on national health surveys, there are approximately 850,000 persons living with chronic HBV infection.<sup>9</sup> However, estimates based on other methods and data yield estimates as high as 2.2 million persons with chronic HBV infection.<sup>10</sup> The prevalence of chronic HBV infection in the United States is driven by foreign-born persons from HBV-endemic regions such as Africa, Asia, and the Pacific Islands.<sup>10</sup> Based on testing from the National Health and Nutrition Examination Survey, the age-adjusted prevalence of hepatitis B core antibody (anti-HBc) in the U.S. population, which indicates past or present infection, decreased steadily from 5.5% during 1988–1994, to 4.8% during 1999–2006, and to 3.7% during 2007–2012 among all persons 6 years of age and older.<sup>9</sup> The overall prevalence of chronic active HBV infection has remained largely constant since 1999. The age adjusted prevalence of anti-HBc and HBsAg together, which indicates chronic active HBV infection, decreased from 0.40% during 1988–1994, to 0.30% during 1999–2006, and remained stable at 0.30% during 2007–2012 among persons 6 years of age and older.<sup>9</sup>

Until recently, hepatitis B was one of the most frequently reported vaccine-preventable diseases in the United States, with 15,000–20,000 cases reported annually to the National Notifiable Diseases Surveillance System (NNDSS). In 2016, 3,218 cases of acute hepatitis B were reported. After correction for underreporting and asymptomatic infections, this represented an estimated 20,917 new infections.<sup>11</sup>

### *Screening and risk factors*

Screening of all pregnant women for HBsAg to identify infants requiring postexposure prophylaxis has been recommended since 1988. Universal infant hepatitis B immunization has been recommended since 1991, and universal adolescent (age 11–12 years) hepatitis B immunization since 1995.<sup>12,13</sup> In the United States, approximately 21,000 HBsAg-positive women give birth annually.<sup>14</sup> Without postexposure prophylaxis to prevent perinatal HBV infection, it is estimated that HBV transmission would occur in 36% of infants born to HBsAg-positive women.<sup>15</sup> Furthermore, before the implementation of universal infant hepatitis B immunization, an additional 16,000 children younger than 10 years old were infected annually in the United States through exposure to HBsAg-positive household members or community contacts.<sup>16</sup> Populations with the highest rates of these early childhood infections included Alaska Natives, children of Pacific Islander parents, and children of first-generation immigrants from countries where HBV is of intermediate or high endemicity.<sup>17–19</sup>

Among persons who reported risk behaviors/exposures in 2016, the most frequently reported risk behavior/exposure for acute, symptomatic hepatitis B was injection drug use (34%), followed by sex with multiple partners (30%).<sup>11</sup> More than half of persons with newly acquired hepatitis B were previously seen in medical settings where hepatitis B vaccine is routinely recommended, such as sexually transmitted disease (STD) treatment clinics or drug treatment centers.<sup>14</sup>

Hepatitis B vaccination is the most effective means to prevent HBV infection and its consequences. Since the hepatitis B vaccines were licensed in the United States in 1982, the number of acute HBV infections has declined from 9.6 per 100,000 in 1982 to 1.0 per 100,000 in 2016.<sup>11,20</sup> Screening of all pregnant women for HBV, universal vaccination of infants, and postexposure prophylaxis provided to infants born to HBsAg-positive women are effective public health strategies to reduce the prevalence of HBV infection and risk of transmission. Healthcare providers should also assess the need for hepatitis B vaccination in all adults and vaccinate all adults who report risks for HBV infection as well as adults seeking protection from HBV infection who do not acknowledge a risk factor.

## **III. Importance of Rapid Identification**

Rapid identification and prompt reporting of cases of acute hepatitis B is important because measures such as postexposure prophylaxis can be taken to prevent transmission to other persons. Although outbreaks of hepatitis B are unusual, rapid recognition allows for identification of the source and prevention of further transmission. In addition, identification of risk behaviors/exposures for infection provides a means to assess the effectiveness of hepatitis B immunization activities in the community and identify missed opportunities for immunization.

In most states, HBsAg positivity is a laboratory-reportable condition. Reporting of HBsAg-positive persons facilitates timely immunization of contacts. For HBsAg-positive pregnant women, reporting allows the initiation of case management to ensure prevention of perinatal HBV transmission (see “Postexposure prophylaxis” below). In 2003, chronic HBV infection became nationally notifiable and is reportable by state health departments to NNDSS. All states are encouraged to report chronic hepatitis B infection. States should develop registries of persons with HBsAg-positive laboratory results to facilitate reporting to NNDSS (see “Registries/databases for HBsAg-positive persons” below) and their contacts should be screened, vaccinated, linked to care, and offered postexposure prophylaxis, as appropriate.

### *Postexposure prophylaxis*

Hepatitis B immune globulin (HBIG) is prepared from human plasma that is known to contain a high titer of antibody to HBsAg (anti-HBs). The plasma from which HBIG is prepared is screened for HBV, hepatitis C virus (HCV), and human immunodeficiency virus infections. Since 1999, all products available in the United States have been manufactured by methods that inactivate HCV and other viruses. A regimen combining hepatitis B vaccine and HBIG is 85%–95% effective in preventing HBV infection when administered to infants born to HBsAg-positive mothers within 12 hours of birth and followed by the hepatitis B vaccine series.<sup>21</sup> Regimens involving either the hepatitis B vaccine series or multiple doses of HBIG alone are 70%–75% effective in preventing HBV infection.<sup>21</sup> Postexposure prophylaxis with hepatitis B vaccine and HBIG should be given to infants born to HBsAg-positive mothers and others (e.g., healthcare personnel after occupational exposure to HBsAg-positive blood) depending on their

vaccination and vaccine response status. Although the postexposure efficacy of the combination of hepatitis B vaccine series and HBIG has not been evaluated for occupational exposure, it can be presumed that the increased efficacy of this regimen observed in the perinatal setting compared with HBIG alone would apply to these exposures.

## IV. Importance of Surveillance

Disease surveillance is used to 1) identify contacts of case-patients who require postexposure prophylaxis; 2) detect outbreaks; 3) identify infected persons who need counseling and referral for medical management; 4) monitor disease incidence and prevalence; and 5) determine the epidemiologic characteristics of infected persons, including the source of their infection, to assess and reduce missed opportunities for vaccination.

## V. Disease Reduction Goals

The primary goal of hepatitis B vaccination is to prevent chronic HBV infection. However, because such a high proportion of persons with chronic HBV infection are asymptomatic and the consequences are not seen for many years, monitoring the direct impact of prevention programs on the prevalence of chronic infection is difficult. Consequently, the disease reduction goals that have been established for hepatitis B are a combination of process and disease outcome measures. Because most HBV infections among children younger than 10 years of age are asymptomatic, programs targeting infants and children are best evaluated by measuring vaccination coverage and the prevalence of HBsAg or anti-HBc as markers of HBV infection.<sup>22,23</sup> As most acute HBV infection is asymptomatic among children, measuring reduction in acute infections is less useful. In older age groups, monitoring the incidence of acute disease as well as measuring vaccine coverage levels provides data useful for measuring the effectiveness of prevention programs.

*Healthy People 2020* disease reduction goals have been established for the United States.<sup>24</sup> Disease reduction goals include reducing the estimated number of chronic HBV infections in infants and children 1–24 months of age from 799 cases in 2007 to 400 cases in 2020 and the number of new hepatitis B cases reported among persons 2–18 years of age from 0.1 new symptomatic cases per 100,000 in 2007 to zero cases in 2020. *Healthy People 2020* vaccination goals for infants and children include setting a target coverage level for infants 0–3 days of age who receive the initial birth dose of hepatitis B vaccine from 70.6% in 2012 to 85% in 2020 and a target coverage level for infants 19–35 months of age who complete the 3-dose hepatitis B vaccination series from 89.7% in 2012 to 90% in 2020.<sup>24</sup> Based on 2017 data, vaccination coverage for infants 0–3 days of age who receive the birth dose of hepatitis B vaccine is 73.6% while the vaccination coverage level for infants 19–35 months of age who receive at least 3 doses of hepatitis B vaccine is 91.4%.<sup>25</sup>

Disease reduction goals for adults 19 years of age and older include reducing the rate of acute hepatitis B from 2.0 cases per 100,000 in 2007 to 1.5 cases per 100,000 in 2020. Among adults in groups at high risk, disease reduction goals include reducing the number of acute hepatitis B infections in persons who inject drugs from 285 cases in 2007 to 215 cases in 2020 and reducing the number of acute hepatitis B infections among men who have sex with men from 62 cases in 2007 to 45 cases in 2020.<sup>24</sup>

## VI. Case Definition

Case definitions for hepatitis B are important to inform accurate data surveillance. The following case definitions for acute hepatitis B, chronic hepatitis B virus infection, and perinatal HBV infection have been adopted by the Council of State and Territorial Epidemiologists.<sup>26–28</sup> Stringent case definitions based on “definite” acute HBV infection allow extrapolation and estimation of acute HBV infection rates in the United States: thus, each reported definite case is thought to represent 6.5 other cases of acute HBV.<sup>29</sup>

### *Hepatitis B, acute (effective 2012)*

#### **Clinical case definition**

An acute illness with

- a. a discrete onset of symptoms\* **AND**
- b. jaundice or elevated serum alanine aminotransferase levels (>100 IU/L).

*\*A documented negative HBsAg laboratory result within 6 months prior to a positive test (either HBsAg, hepatitis B e antigen [HBeAg], or HBV nucleic acid testing [NAT] including genotype) result does not require an acute clinical presentation to meet the surveillance case definition.*

#### Laboratory criteria for diagnosis

- HBsAg positive **AND**
- Immunoglobulin M (IgM) antibody to hepatitis B core antigen (IgM anti-HBc) positive (if done)

#### Case classification

**Confirmed:** a case that meets the clinical case definition and is laboratory confirmed, and is not known to have chronic hepatitis B.

#### *Chronic hepatitis B virus infection (effective 2012)*

##### Clinical description

Persons with chronic HBV infection may have no evidence of liver disease or may have a spectrum of disease ranging from chronic hepatitis to cirrhosis or liver cancer. Persons with chronic infection may be asymptomatic.

##### Laboratory criteria for diagnosis

- IgM anti-HBc negative **AND** a positive result on one of the following tests: HBsAg, HBeAg, or NAT for HBV DNA (including qualitative, quantitative, and genotype testing) **OR**
- HBsAg positive or NAT for HBV DNA positive (including qualitative, quantitative, and genotype testing) or HBeAg positive 2 times at least 6 months apart (Any combination of these tests performed 6 months apart is acceptable.)

##### Case classification

**Confirmed:** a case that meets either laboratory criterion for diagnosis.

**Probable:** a case with a single HBsAg-positive or HBV DNA-positive (including qualitative, quantitative, and genotype testing) or HBeAg-positive laboratory result when no IgM anti-HBc results are available.

**Comment:** Multiple laboratory tests indicative of chronic HBV infection may be performed simultaneously on the same patient specimen as part of a “hepatitis panel.” Testing performed in this manner may lead to seemingly discordant results, e.g., HBsAg negative and HBV DNA positive. For purposes of this case definition, any positive result among the three laboratory tests mentioned above is acceptable, regardless of other testing results. Negative HBeAg results and HBV DNA levels below positive cutoff level do not confirm the absence of HBV infection.

#### *Perinatal hepatitis B virus infection (effective 2017)*

##### Clinical description

Perinatal hepatitis B in a child  $\leq 24$  months of age may range from asymptomatic to fulminant hepatitis.

##### Laboratory criteria for diagnosis consists of one or more of the following

- Positive HBsAg test (only if at least 4 weeks after last dose of hepatitis B vaccine) **OR**
- Positive HBeAg **OR**
- Positive HBV DNA

##### Case classification

**Confirmed:** Child born in the United States or a United States territory to a HBV-infected mother and positive for HBsAg at  $\geq 1$  month of age and  $\leq 24$  months of age **OR** positive for HBeAg or HBV DNA at  $\geq 9$  months of age and  $\leq 24$  months of age.

**Probable:** Child born in the United States or a United States territory and positive for HBsAg at  $\geq 1$  month of age and  $\leq 24$  months of age **OR** positive for HBeAg or HBV DNA at  $\geq 9$  months of age and  $\leq 24$  months of age, but whose mother’s hepatitis B status is unknown.

**Comment:** Infants born to HBsAg-positive mothers should receive the first dose of hepatitis B vaccine and HBIG within 12 hours of birth, followed by the second and third doses of vaccine at 1 and 6 months of age, respectively, if receiving the single-antigen vaccine. Scheduling will be different if the infant received a combination vaccine or if the infant weighed <2,000 grams at birth. Postvaccination serologic testing for HBsAg and anti-HBs (antibody to HBsAg) is recommended at age 9–12 months (or 1–2 months after the final dose of the vaccine series, if the series is delayed). If the initial dose of the hepatitis B vaccine and HBIG are delayed for more than 1 month after birth, testing for HBsAg may determine if the infant is already infected.

## VII. Laboratory Testing

Diagnostic tests used to confirm hepatitis B virus (HBV) infection include serologic testing, genotyping and subtyping (in outbreak investigations), and occasionally PCR-based assays to amplify/quantify and determine the sequence of viral genomes.

Refer to Chapter 22, “Laboratory Support for Surveillance of Vaccine-Preventable Diseases (<https://www.cdc.gov/vaccines/pubs/surv-manual/chpt22-lab-support.html>) for detailed information on laboratory testing for hepatitis B.

### *Specimen collection*

Specimen collection and shipping are important steps in obtaining laboratory diagnosis or disease confirmation. Guidelines have been published for specimen collection and handling for viral and microbiologic agents. Information is also available on using CDC laboratories as support for reference and disease surveillance; this includes:

- a central website (<https://www.cdc.gov/laboratory/specimen-submission/index.html>) for requesting lab testing;
- the form required for submitting specimens to CDC (see Appendix 23, Form # CDC 50.34);
- information on general requirements for shipment of etiologic agents (Appendix 24; <https://www.cdc.gov/vaccines/pubs/surv-manual/appx/appendix24-etiological-agent.pdf>) and
- the CDC Infectious Diseases Laboratories Test Directory (<https://www.cdc.gov/laboratory/specimen-submission/form.html>), which provides an online test that contains not only a list (<https://www.cdc.gov/laboratory/specimen-submission/list.html>) of orderable tests for that institution, but also detailed information on appropriate specimen types, collection methods, specimen volume, and points of contact.

## VIII. Reporting and Case Notification

### *Case reporting within a jurisdiction*

In the United States, case reports of viral hepatitis are classified as hepatitis A, acute hepatitis B, acute hepatitis C, perinatal HBV infection, chronic hepatitis B, and hepatitis C, past or present, and perinatal HCV infection. Serologic testing is necessary to determine the etiology of viral hepatitis, and case reports should be based on laboratory confirmation (see Section VII). Each state and territory (jurisdiction) has a list of reportable diseases and conditions of public health importance.<sup>30,31</sup> This list also includes persons or groups who are responsible for reporting, such as healthcare providers, hospitals, laboratories, and other institutions. Persons reporting these conditions should contact their state/jurisdiction health department for jurisdiction-specific reporting requirements. The CDC Viral Hepatitis Case Report worksheet is included as Appendix 6, to serve as a guide for data collection during investigation of reported cases.

### *Case notification to CDC*

Case notifications of acute hepatitis B, chronic HBV infection, perinatal HBV infection, and other reportable diseases are transmitted weekly by the state/jurisdiction health departments to CDC through NNDSS. NNDSS core data elements include basic information (excluding personal identifiers)—age, race/ethnicity, sex, date of onset, date of report, and county of residence. The National Electronic Telecommunications System for Surveillance (NETSS) includes extended data elements, e.g., clinical data, laboratory results, and exposure history. However, notifications of these extended data elements are often incomplete. (For example, in 2016, 52% of acute, symptomatic hepatitis B cases were reported

in the United States without risk exposure/behavior information.)<sup>11</sup> The Division of Viral Hepatitis has developed an extended data collection worksheet, included as Appendix 6 to serve as a guide for data collection for information about symptoms, risk behavior/exposures, and serologic data. This worksheet can be used for case investigation, and data can be directly entered into the state's electronic reporting system. Jurisdictions that report cases through the National Electronic Diseases Surveillance System<sup>32</sup> and Emerging Infections Program<sup>33</sup> (Enhanced Hepatitis Surveillance) infrastructure can also collect data elements using this worksheet. Case notifications should not be delayed because of incomplete information or lack of confirmation. Data can be updated electronically as more information becomes available. The state/jurisdiction in which the patient resides at the time of diagnosis should submit the case notification to CDC.

## IX. Vaccination

For specific information about the use of hepatitis B vaccines, refer to The Pink Book [<https://www.cdc.gov/vaccines/pubs/pinkbook/index.html>], which provides recommendations, including vaccine use and scheduling, immunization strategies for providers, vaccine content, adverse events and reactions, vaccine storage and handling, and contraindications and precautions.

## X. Enhancing Surveillance

Establishing surveillance for acute hepatitis is difficult for several reasons. Five different viruses (A–E) cause viral hepatitis, and the clinical manifestations of the different types of acute hepatitis are similar. Infection with HBV, HCV, and HDV can result in both acute and chronic infection. Therefore, serologic testing is necessary to establish an etiologic diagnosis for persons with symptoms of acute hepatitis and to evaluate case reports of persons who are reported with viral hepatitis. However, a lack of understanding about the epidemiology of these diseases and underutilization of serologic testing could result in significant misclassification in reporting of acute viral hepatitis.

### *Provider education*

Providers should be educated about the importance of performing appropriate serologic tests to determine the etiology of viral hepatitis and reporting all cases of acute hepatitis B, chronic hepatitis B, and perinatal hepatitis B. Case investigations of infected persons provide the best opportunity for postexposure prophylaxis of contacts and for reducing transmission.

### *Case investigation*

Case investigation is essential for determining contacts who are eligible for prophylaxis and for collection of risk factor data. Analysis of risk factor data can identify populations where targeted interventions may be needed.

### *Laboratory reporting*

Laboratories should be encouraged to report all persons with serologic markers of acute or chronic hepatitis B to the state or local health department. All IgM anti-HBc– and HBsAg-positive results should be reported. To facilitate reporting, these laboratory results could be included in the state's list of laboratory-reportable conditions.

### *Monitoring surveillance indicators*

Regular monitoring of surveillance indicators, including date of report, timeliness, and completeness of reporting, may identify specific areas of the surveillance and reporting system that need improvement. Important program indicators that can be monitored through the surveillance, reporting and case investigation system include the following:

- Characteristics of cases of acute hepatitis B that occur in children and adolescents and missed opportunities for vaccination.
- Characteristics of cases of acute hepatitis B in which death has occurred.
- Characteristics of cases of acute hepatitis B in persons reporting a history of vaccination.
- Characteristics of cases of acute hepatitis B in persons over 70 years of age.



- Characteristics of cases of acute hepatitis B associated with healthcare transmission.
- Characteristics of cases of perinatal hepatitis B.

### *Registries/databases for HBsAg-positive persons*

Reporting of HBsAg-positive test results and establishment of databases/registries for HBsAg-positive persons is encouraged. When any type of database is established, the confidentiality of individual identifying information needs to be ensured according to applicable laws and regulations. Computerized databases of persons with HBsAg-positive results can be used to:

- Distinguish newly reported cases of infection from previously identified cases and facilitate reporting of chronic hepatitis B;
- Facilitate case investigation and follow-up of persons with chronic HBV infection;
- Provide local, state, and national estimates of the proportion of persons with chronic HBV infection who have been identified.

### *Hospital-based reporting*

Hospitals and infection control practitioners should be encouraged to report all persons with acute viral hepatitis (ICD-10 code B16) and all births to HBsAg-positive women.

### *Streamlining reporting using electronic methods*

Although many surveillance systems still rely on paper and pencil for data collection, use of data from sources such as electronic medical records, electronic case reporting,<sup>34–40</sup> and clinical laboratory information systems (LIMS) can significantly improve reporting speed, enhance data quality, and reduce workload.

## **XI. Case Investigation**

Guidelines for investigating a suspected case of acute viral hepatitis include

- determining a discrete onset of illness,
- confirming evidence of acute liver disease (jaundice or elevated aminotransferase levels), and
- obtaining serologic laboratory results.

The minimum recommended elements for investigating cases of chronic HBV infection and perinatal HBV infection include obtaining the serologic laboratory results needed to establish the case. Further investigation to determine the clinical characteristics of these cases may also be considered although it is not required to confirm the case.

### *Information to collect for acute hepatitis B infection*

The following information is epidemiologically important to collect in a case investigation for acute hepatitis B infection.<sup>41,42</sup> Additional information may also be collected at the direction of the jurisdiction/state health department.

- Demographic information
  - Clinical details
  - Date of illness onset
- Symptoms, including jaundice
- Laboratory results
- Vaccination status
- Risk behaviors/exposures
- Contact investigation and prophylaxis

### *Information to collect for chronic hepatitis B infection*

The following information is epidemiologically important to collect in a case investigation for chronic hepatitis B infection.<sup>34,35</sup> Additional information may also be collected at the direction of the jurisdiction/state health department.

- Demographic information
- Laboratory results
- Risk behaviors/exposures
- Pregnancy status. All HBsAg-positive pregnant women should be reported to the Perinatal Hepatitis B Prevention Program manager so that they can be tracked and their infants can receive appropriate case management

The recommended elements of case investigation and follow-up of persons with chronic hepatitis B virus infection are detailed elsewhere.<sup>6</sup> The following should be included:

- Contact investigation and prophylaxis: Provision of hepatitis B vaccination for sexual, household, and other (needle-sharing) contacts of persons with hepatitis B, and counseling to prevent transmission to others
- Counseling and referral for medical management, including
  - assessing for biochemical evidence of chronic liver disease, and
  - evaluating eligibility for antiviral treatment.

#### *Information to collect for perinatal HBV infection*

The following information is epidemiologically important to collect in a case investigation for perinatal HBV infection:

- Demographic information about the child and mother
- Laboratory results
- Birth weight is useful because infants <2,000 grams will require an additional vaccine dose
- Immunization history of the child, including date/time and doses of hepatitis B vaccine and HBIG

Case investigation and follow-up of infants with hepatitis B virus infection should include the following:

- Referral for medical management, including
  - assessing for biochemical evidence of chronic liver disease, and
  - evaluating eligibility for antiviral treatment
- Identification of other susceptible infants and children in the household who require vaccination

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