# Hepatitis B virus vaccination

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- **Despite** advances in **antiviral therapy**, only a **minority** of patients with chronic **hepatitis B** will have a **sustained** response.
- **Thus**, primary **prevention** by **vaccination** to increase herd immunity remains the **main** focus in **controlling HBV** infection.

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- The commonly used **hepatitis B vaccines** have an efficacy of **>90 %** against all HBV serotypes and genotypes.
- Thus, **HBV** infection **can potentially** be **eradicated** through **global vaccination**.
- **Globally**, **vaccine coverage for infants** based upon completion of the third dose of vaccine (HepB3) has **increased** from **3 %** in **1992** to **84 %** in **2015**

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- **While vaccination** represents the **cornerstone** of public health measures to **eradicate HBV**,
- **5 to 10 %** of individuals do **not respond** to currently available vaccines.
- **Thus**, other public health **measures**, including health **education** and **infection control** measures, remain important.

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# INDICATIONS

- **all neonates *regardless*** of **maternal** hepatitis B surface antigen **(HBsAg)** status
- (strong recommendation for **screening** women during their **first prenatal visit**.)

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- The **AASLD** supports **CDC's** recommendation regarding **screening** of high risk groups and **vaccinating** those who are
- ***not already immune or infected***

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- This includes :
- 1)persons with chronically elevated aminotransferases,
- 2)persons needing immunosuppressive therapy,
- 3)Health care workers
- 4)men who have sex with men,
- 5)persons with multiple sexual partners
- 6)Persons with history of sexually transmitted disease,

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- 7)inmates of correctional facilities,
- 8)persons who have ever used injecting drugs,
- 9)patients on dialysis,
- 10)HIV or HCV-infected patients, and
- 11)family members, household members, and
- 12) sexual contacts of HBV-infected persons.
- 13)persons requiring repeated blood or blood product transfusion

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- 14) persons **traveling** to areas with **intermediate to high** levels of **endemic HBV** infection
- Vaccination should **also** be considered for **all international travelers**, **depending** on the
- **behavioral risk** of the **travelers** and

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- 15) adults with diabetes mellitus who are ages 19 to 59
- For older patients with diabetes, vaccination can be administered at the discretion of the treating clinician based on the risk of acquiring HBV

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- Universal vaccination of all newborns, regardless of maternal HBsAg status, is necessary for global eradication of HBV infection
- Countries that have adopted universal vaccination of newborns have experienced a marked reduction in carrier rates as well as complications from HBV including
- hepatocellular carcinoma

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- universal vaccination can prevent
- vertical and horizontal transmission of HBV infection
- as well as the sequel of chronic HBV infection.
- In countries with low endemicity, the benefits
- of universal neonatal vaccination will not be apparent until two to three decades later
- because infection in these countries usually occurs among adolescents and young adults through percutaneous or sexual routes.

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- Vaccination of neonates born to HBsAg-positive mothers is the most important step toward the eradication of chronic HBV infection

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- The standard regimen for neonates born to HBsAg-positive mothers consists of passive and active immunization.
- Hepatitis B vaccine and HBIG are given at the same time at two different sites
- within 12 hours of delivery.
- The neonates should then receive two additional doses of the hepatitis B vaccine at months 1 to 2 and months 6 to 12.
- This regimen has a protective efficacy of 95 %

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- Studies in Taiwan and Hong Kong found that the protective efficacy of hepatitis B vaccine alone was significantly lower (only 75 to 80 %)

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- However, mother-to-child transmission of HBV can still occur when HBIG and the first dose of the HBV vaccine are administered within 24 hours of birth and the remaining course of HBV vaccination is completed.
- These cases of vaccine failure arise when the mothers are HBsAg positive with high serum HBV DNA levels .
- Clinical trials have shown that antiviral therapy administered to HBsAg positive mothers with high viremia starting in the third trimester of pregnancy together with timely administration of HBIG and HBV vaccine can further reduce the risk of mother-to-child transmission

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## Catch-up vaccination

- **vaccination** of **children** who were **born before universal neonatal vaccination**
- **All unvaccinated children** and **adolescents <19** years should receive the HBV vaccine series

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## Post-vaccination testing

- the current **hepatitis B vaccines** have a **response** rate of **95 percent**.
- **Thus**, **routine post-vaccination** testing to document anti-HBs is **unnecessary**, except
- in **health care** workers,
- patients on chronic **hemodialysis**,
- other **immunocompromised** patients (**including** those with **HIV** infection)
- individuals who are at **risk for recurrent exposure** to hepatitis B virus (**spouses or sexual partners** of carriers and **infants of carrier mothers**).

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- Testing should be performed **one to two months after** completion of the primary vaccination series except for
- infants born to HBsAg-positive mothers in
- whom testing should be performed at
- age 9 to 12 months of age or
- one to two months after the last dose of vaccine **if immunization is delayed**

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- **Non-responders** should complete a **second three-dose** vaccine series
- which is successful in about **50 to 70 %.**
- **Retesting** for **anti-HBs** should be **repeated** after the second vaccination series.
- **Non-responders to the second** course of vaccine should be **tested for HBsAg**

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- As most of these children are school-age, catch-up vaccination permits these children to be immunized before they reach adolescence when they are at risk of infection through
- sexual exposure and injection drug use

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- Steady sexual partners of individuals with chronic HBV infection should be tested and vaccinated against hepatitis B if found to be seronegative.

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- **Health care** practitioners with an **anti-HBs** concentration **less than 10** milli-IU/mL should
- receive **another three** appropriately scheduled doses of the vaccine **with serological testing** performed **one to two months after the third** dose.

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- **Individuals** with an **anti-HBs** level **less than 10** milli-IU/mL
- **after the second series** should be **tested** for **HBsAg** and **anti-HBc**.
- **Those** who are **not infected *and***
- who had **not responded** to the vaccine are
- considered **susceptible to HBV** infection
- and must be **counseled** about **prevention** and transmission of hepatitis B.
- **These individuals**, upon **known or likely** exposure, should **receive HBIG**.

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- **Individuals** who are **anti-HBc-positive** and **HBsAg-negative** require **no treatment** .
- In addition, **HBV vaccination** is generally **not required**, ***Unless*** there is **concern** that the
- 1)patient has a **false positive anti-HBc** (the **health care provider** is from a **low endemic area** and has **no risk factors** for HBV) ***or***
- 2)**immunocompromised** patients **including** those with **HIV**, since **these patients may have resolved HBV** infection and **loss of anti-HBs**, and **would respond to vaccination**

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- 3)Patients on chronic hemodialysis and
- 4)patients requiring repeated blood or blood products
- **Anti-HBs** titers should be **checked annually**
- and **booster** doses administered **as needed**.

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- **Patients with chronic liver disease**
- **Vaccination** should be administered **as early as possible**
- because **response** rates to HepB vaccine are
- low in patients with **decompensated cirrhosis** (around 36 %) and
- those who have undergone liver **transplantation** (around 8 to 11 % )

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- Patients who have **serologic** markers of **past HBV infection** (**anti-HBc** and **anti-HBs** positive) do **not need** HBV **vaccination** even if they have low titers of anti-HBs.
- **Such** patients will be **able** to mount an appropriate **immune response** should they be **rechallenged** with HBV.

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- Persons with **isolated anti-HBc** (HBsAg and anti-HBs negative) who **have risk factors** for **HBV** infection including:
- having **grown** up in **high endemic** areas
- likely had **prior exposure** and do **not require** vaccination.
- **However,** persons who are **positive only for anti-HBc** and **who** are from a **low endemic** area **with no risk factors** for HBV **should** be **given the full series** of hepatitis **B vaccine**

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## PRE VACCINATION SCREENING

- The **role** of **pre-vaccination screening** is to **identify** individuals who
- do **not require vaccination** and thereby **reduce unnecessary vaccination**.
- The **need for** pre-vaccination **screening** should be **guided** by
- the **likelihood** that an **individual** has been **exposed to HBV**
- **Pre-immunization** testing is **cost-effective** in populations in which the **prevalence** of infection **exceeds 30 %**

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- In **non-endemic** areas, pre-vaccination **screening** is **unnecessary** since the **costs** of **screening** outweigh that of savings on the vaccine.
- **Exceptions** are patients in **high-risk groups** in whom **screening** should be performed
- by **testing** for **anti-HBs** antibodies.
- **Additional testing** for **HBsAg** among **high risk** groups is **recommended** by the **CDC** to **identify** those who might **already be infected**.

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- In **endemic areas**, **pre-vaccination screening** should be performed in **adults** since the
- **prevalence** of **past** and **current** infection may **exceed 50 %**
- **Pre-vaccination screening** in these high risk populations is also **important** in i**dentifying** infected persons who may benefit from **treatment**.

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- In **these countries**, **screening** can be performed by a single test for **anti-HBc alone**,
- which will detect individuals with past or current infection, ***or***
- by a **combination** of **HBsAg** and **anti-HBs**.
- **While** a **single** test for **anti-HBc** may be more **economical,**
- it does **not differentiate *carriers* from** individuals who **have recovered** from previous infection.

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- In **endemic** areas, the **combination** of **HBsAg** and **anti-HBs** testing is **preferred**.
- This strategy will **also allow** the **identification** of **carriers** who can be **followed** and **treated**.

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- **Vaccines** should be administered
- **intramuscularly** since **deposition** of the vaccine into **adipose tissue** result in a **lower seroconversion** rate .
- Thus, the **deltoid** is the preferred site in **adults**
- while the **vastus late**ralis is preferred in **infants**.
- **Longer needles** should be used in **overweight** individuals

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## What to do about a missed dose

- **Longer than recommended intervals** between doses do **not reduce final antibody** concentrations,
- **although protection** might **not** be attained **until** the recommended **number of doses** has been administered .
- **Thus**, an **interruption** in the vaccination schedule does **not require**
- **restarting** the entire series of vaccination ***or*** adding **extra doses** .

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- **If** the vaccination series is **interrupted after the first** dose,
- the **second** dose should be administered **as soon as** possible
- The **second and third** doses should be **separated** by an interval of at **least two months**.
- **If** only the **third dose** is delayed, it should be administered **when convenient**.
- **Although protective anti-HBs** titers may be attained in **some** persons **after only one or two doses** of vaccine,
- completion of the full course (**three doses**) of vaccine is recommended **to maximize** the **anti-HBs titer *and* duration** of protection.

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## Efficacy

- A **positive immune** response to the vaccine is **defined** as the development of hepatitis B surface antibody (**anti-HBs**) at a titer **of >10** milli-IU/mL.
- **overall response** rate is about **95 %** in **healthy adults.**
- The rate **decreases** with increasing **age** to
- **86 %** in the **fourth decade** and
- **47 %** in the **sixth decade**

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- The **response** rate is slightly **lower** in :
- obese individuals,
- smokers,
- men,
- significantly **lower** in patients with
- cirrhosis
- chronic renal failure,
- organ transplant recipients,
- children with celiac disease,
- immunosuppressed patients.

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- In patients on chronic **hemodialysis**, **response** rate to recombinant vaccines is **50 to 60 %**
- **Despite** the **lower seroconversion** rate,
- the **risk** of hepatitis **B infection** is **70 % lower** in the **vaccinated** patients when **compared**
- with **non-vaccinated** patients undergoing chronic **hemodialysis**

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## Duration of protection

- **Although anti-HBs titers decrease with time**,
- the **duration** of protection is **long**.
- Protection persist for up to **30 years**
- **Protection** from **clinical disease** is felt to occur **even** in the setting of **declining** or **undetectable** anti-HBs levels,
- due to the priming of **memory cells**, which are capable of eliciting an anamnestic response **when challenged**, and **long-lasting cellular immunity**

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- A high antibody concentration following primary vaccination may be associated with an anamnestic response later in life.
- As an example, protection appears to extend beyond 15 years in vaccinees who had a high titer anti-HBs response (>100 milli-IU/mL) after the initial course of vaccination

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## Booster doses

- In most countries, a booster dose of vaccine is **not routinely** recommended for
- **immunocompetent** children and adults **who have responded** to a complete three-dose vaccine Series
- **However, booster** doses should be administered to certain patients who are at **high risk** for both **waning immunity** and **HBV transmission**

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- booster vaccination is recommended for
- patients on **hemodialysis**, and
- other **immunocompromised** persons that the need for a booster dose should be **assessed annually** and a **booster dose administered** if the antibody level **declines to <10** milli-IU/mL

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## Adverse reactions

- The most common adverse reaction associated with recombinant hepatitis B vaccines (non-adjuvanted) is
- **soreness** over the site of **injection**, which occurs in **fewer than 25 %** of the vaccinees.
- **Other** adverse reactions reported by **1 to 3 %** of vaccinees include
- **low grade fever**, **malaise, headache, joint pain** and **myalgia**.
- These adverse reactions are usually mild and do not result in any serious clinical sequel.
- Hepatitis B vaccines have **no teratogenic** effects and can be administered during pregnancy

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## Management of nonresponders

- There are three main groups of vaccine non-responders:

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- Patients with **underlying medical conditions** such as chronic **kidney** disease and **immunosuppressed** states.
- In patients undergoing **hemodialysis**, **response** rate to the **standard dose of vaccine** is between **50 and 60 %.**
- This can be **improved to above 70 % by doubling** the dose of the vaccine
- The response rate can also be improved by **intradermal** administration of the vaccine
- The **current policy** for patients with **chronic renal failure** is to **vaccinate** them **before** commencement of **hemodialysis**.

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- In **second group** of non-responders **lack of response** appears to be **genetically** determined.
- these individuals **lack** a dominant **response gene** that controls the **production of anti-HBs**.
- The **absence of this gene** may be marked by **two extended HLA haplotypes**
- Individuals with **celiac disease** also appear to have a **diminished** response to **HBV vaccine**

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- The **third** group failed to respond as a result of **technical errors** including :
- **intra-gluteal** injection or
- **inappropriate storage** conditions such as
- inadvertent freezing of vaccines during shipment

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## Recommendation

- The current recommendation for **all healthy non-responders** is to **administer *one or more additional doses.***
- An adequate antibody **response** is seen in **15 to 25 %** after **one** additional dose and in 50 % after three additional doses

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- Individuals **who fail to respond** after **three additional** doses of vaccine are **unlikely** to **benefit** from **further vaccination**.
- **However**, these individuals may **still** mount an **adequate immune** response and **recover from HBV infection.**

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- Individuals who **fail** to respond **after two courses of HepB vaccine** should be **tested** for **HBsAg**
- Non-responders **who test negative for HBsAg** should be **educated** on how to **prevent HBV** infection, including the need for hepatitis B immune globulin (**HBIG**) if they have an **exposure to blood** or other body fluids of a **person who is HBsAg-positive**.

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- Additional strategies for vaccinating non-responders continue to be studied.
- In a report that included 48 HepB vaccine non-responders, vaccination with a double dose of the combined hepatitis A and B vaccine (Twinrix) at zero, one, and six months led to protective anti-HBs levels in 59 and 95 percent after the first and third dose, respectively
- These results support that non-responders should receive a second course of HepB vaccine

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## VACCINE-INDUCED HBV S ESCAPE MUTANTS

- **HBV S gene mutants** have been described in **infants** who were **infected with hepatitis B** despite an **adequate anti-HBs** response to hepatitis B vaccination.
- These mutants have been observed in many parts of the world including **China, Singapore, Taiwan, Japan, Italy, and Africa**
- The **most common mutation** involves a **glycine to arginine substitution** at codon 145 in the **"a" determinant of HBsAg**.

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- **This mutation decreases binding of HBsAg to anti-HBs** and may explain why these infants develop "escape" infection.
- The G145R **mutation has also** been observed in **liver transplant** recipients who developed **recurrent HBV infection despite HBIG** prophylaxis
- These **mutants** can be detected in **less than 5 % of all infants** who have **received HBV vaccination** and
- **only 10 to 40 %** of the **vaccine failures** can be attributed to **HBV S mutants**.

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- Most reports found that the HBV S mutations were not detected in the maternal carriers, suggesting that the mutations were selected by immune pressure (vaccine and/or HBIG).
- A study from Taiwan demonstrated these mutants in infants who received HepB vaccine without HBIG indicating that the vaccine alone was sufficient to select the mutations
- Experiments in chimpanzees confirmed that these mutants are infectious.

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- There are concerns that the vaccine escape mutants have become more prevalent over time,
- causing acute infections in individuals who were previously vaccinated
- However, long-term follow-up of vaccination programs have not observed a progressive decline in the efficacy of HepB vaccines.
- A report from Taiwan found that the prevalence of HBV S mutants in HBV DNA positive children increased from 8 percent (8 of 103) in 1984 to 19.6 percent (10 of 51) in 1989, peaked at 28 percent (9 of 32) in 1994, and remained at 23 percent (3 of 13) in 1999

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- However, long-term follow-up of vaccination programs have not observed a progressive decline in the efficacy of HepB vaccines or an increase in the prevalence of HBV S mutants among the pediatric population.
- A report from Taiwan found that the prevalence of HBV S mutants among children <15 years surveyed in 1984 and 2004 decreased from 0.67 to 0.10 percent, and prevalence of HBsAg decreased from 9.6 to 0.5 percent

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- Based upon available data, the benefits of conventional HepB vaccine far outweigh the concerns of HBV S escape mutants and vaccination programs should not be deterred because of these concerns.
- However, continued monitoring is necessary to determine if the prevalence of these mutants is increasing and if the protective efficacy of conventional vaccines is maintained.
- There is clearly a need for further research to develop vaccines that are more effective and which are capable of circumventing these mutations.

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## Ways to enhance immunogenicity

- **Intradermal inoculation**
- Intradermal inoculation appears to be more immunogenic than intramuscular injections, but is technically more difficult to administer
- **New adjuvants**
- The **concomitant** administration of **interferon alpha, interferon gamma, or interleukin-2** with conventional hepatitis B vaccines augmented the immune response

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- Several studies have evaluated intradermal versus intramuscular vaccination in patients with chronic kidney disease on dialysis (a group that generally has a suboptimal response to vaccination).
- A meta-analysis of 12 studies concluded that an initial response was more likely with the intradermal approach but the difference was no longer significant with follow-up (6 to 60 months)
- In other studies, the increased efficacy of intradermal inoculation was also evident in intramuscular vaccine nonresponders.
- In one study, for example, 50 hemodialysis patients were revaccinated either intradermally or intramuscularly with a total dose of 80 mcg of recombinant vaccine

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- In one study, for example, 50 hemodialysis patients were revaccinated either intradermally or intramuscularly with a total dose of 80 mcg of recombinant vaccine
- Seroconversion rates at 20 months were much higher in the group vaccinated intradermally (54 versus 0 percent)
- Frequent low dose intradermal administration of hepatitis B vaccine may maintain protective anti-HBs levels in hemodialyzed patients who did not have an adequate immune response to hepatitis B vaccine

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- **New adjuvants**
- The concomitant administration of interferon alpha, interferon gamma, or interleukin-2 with conventional hepatitis B vaccines augmented the immune response in patients undergoing hemodialysis in
- some studies
- Subsequently, adjuvanted hepatitis B vaccines have been developed.
- An adjuvanted recombinant hepatitis B vaccine (HEPLISAV) consisting of HBsAg with an adjuvant
- immunostimulatory phosphorothioate oligodeoxyribonucleotide (HBV-ISS) has received conditional approval in the United States for adults 18 years of age and older.
- Another vaccine combines HBsAg with an adjuvant containing 3'-deacylated monophosphoryl lipid A and alum (AS04) to enhance the immunogenicity.
- This vaccine is approved in Europe for patients older than 15 years of age with renal insufficiency, including those who are prehemodialysis and those on hemodialysis.
- The use of the HBsAg/AS04 vaccine has been supported by several studies.

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- **New adjuvants**
- In one study involving 105 individuals aged 20 to 60 years who were nonresponders to commercially available hepatitis B vaccine, HBsAg/AS04 vaccine was compared with revaccination with commercially available hepatitis B vaccine
- After three doses, the response rate among those who received the HBsAg/AS04 vaccine was 98 percent compared with 68 percent among those who received the conventional vaccine.
- The geometric mean anti-HBs titers (GMT) were also significantly higher than the group that received conventional vaccine
- In another study, patients undergoing maintenance renal dialysis were vaccinated with four doses of HBV-AS04 vaccine.
- At the completion of the vaccination schedule, 84 percent developed anti-HBs antibody of ≥10 milli-international units/mL.
- Other studies have reported a two-dose regimen for this vaccine with superior GMTs compared to three doses of conventional vaccine.
- It is anticipated that a simpler vaccination schedule may increase compliance with completion of the vaccination regimen

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- **Live recombinant vaccines**
- Results of studies using live recombinant vaccinia virus that **express the HBV S gene** in **chimpanzees** have been promising
- **DNA vaccines**
- Vaccines that contain **naked DNA** (plasmids that contain the HBV S gene) can be injected intramuscularly.

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- **Pre-S vaccines**
- The **HBV encodes three envelope proteins**.
- The **large S protein** includes:
- the pre-S1, pre-S2 and S regions,
- the **middle S protein** includes:
- the pre-S2 and S regions,
- the **small S protein** encodes the S region only.
- Studies in **mice** found that **addition** of **pre-S1 or pre-S2** regions may circumvent nonresponsiveness to HBsAg

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## CONTRAINDICATIONS AND PRECAUTIONS

- HBV **vaccination** is **contraindicated** in individuals with a
- history of **hypersensitivity to yeast** or to any vaccine component
- Acute **moderate to severe illness** is a precaution to HBV vaccination
- Vaccination generally **should be postponed** until after recovery
- However, decisions should be individualized.

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- **DNA vaccines**
- Vaccines that contain naked DNA (plasmids that contain the HBV S gene) can be injected intramuscularly.
- HBsAg is expressed in the muscle cells.
- The intracellular production of HBsAg stimulates production of anti-HBs.
- In addition, the newly synthesized HBsAg may be degraded within the muscle cells to form peptides, which are expressed on the cell surface together with HLA class I molecule stimulating the production of cytotoxic T-cells
- The protective efficacy of the HBV DNA vaccine was demonstrated in two chimpanzees that were vaccinated at birth and boosted at 6 and 24 weeks
- Although the production of anti-HBs was transient, both animals developed an anamnestic antibody response when challenged with an inoculum containing infectious doses of HBV at 33 weeks,
- and did not develop any markers of HBV infection.
- There are no published data from human trials.

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- **Pre-S vaccines**
- The HBV encodes three envelope proteins. The large S protein includes the pre-S1, pre-S2 and S regions, the middle S protein includes the pre-S2 and S regions, and the small S protein encodes the S region only.
- All three regions contain immunogenic T and B cell epitopes.
- Studies in mice found that addition of pre-S1 or pre-S2 regions may circumvent nonresponsiveness to HBsAg.
- Preliminary clinical studies found that addition of pre-S2 region to conventional vaccine did not reduce the nonresponse rate in humans
- However, a study on 100 nonresponders found that revaccination with a vaccine that contain pre-S1, pre-S2 and S regions induced higher rates of response than revaccination with another course of conventional vaccine
- Sixty-nine percent of the vaccinees seroconverted after one single dose of the vaccine and one vaccinee seroconverted after a booster dose

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- **Pre-S vaccines**
- These encouraging results remain to be confirmed in other studies.
- Another study reported positive response among the majority of nonresponders to yeast-derived, single epitope recombinant vaccine after two doses of hepatitis B vaccine containing pre-S2 epitopes
- A third study showed a response rate of 71 percent after four doses of this vaccine among patients with chronic renal disease of whom about 75 percent were on chronic dialysis
- In addition to its potential use in conventional vaccine nonresponders, there were reports that this new class of vaccine resulted in high mean titers of anti-HBs earlier in the course of vaccination.
- This suggests higher immunogenicity for this class of vaccines compared to conventional yeast-derived recombinant vaccines
- Currently, these vaccines are licensed for use in Israel, Western Europe and some Asian countries

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- The preferred regimen for infants who remain susceptible after the primary infant series is one dose of HepB vaccine followed by measurement of anti-HBs and HBsAg one to two months later
- This approach is supported by studies in which >94 % of infants born to HBsAg-positive women achieved anti-HBs≥10 mIU/mL with one additional dose of HepB vaccine

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- HBsAg-negative infants whose anti-HBs remains <10 mIU/mL after the first additional dose of HepB vaccine should receive two more doses, separated by at least eight weeks,
- with measurement of anti-HBs and HBsAg one to two months later. In a cohort study, all 45 HBV-susceptible children who did not respond to perinatal HepB immunization
- responded to a second HepB vaccine series, and >70 percent had protective titers four years later

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- An alternative regimen for infants who remain susceptible after the primary infant series is three doses of HepB vaccine (at zero, one to two, and six months)
- followed by measurement of anti-HBs and HBsAg one to two months after the third dose.
- The alternative regimen may be warranted depending on clinical circumstances or family preference

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- HBsAg-negative children whose anti-HBs levels remain <10 mIU/mL after two complete series of HepB vaccines are considered to be "non-responders" and susceptible to HBV.

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