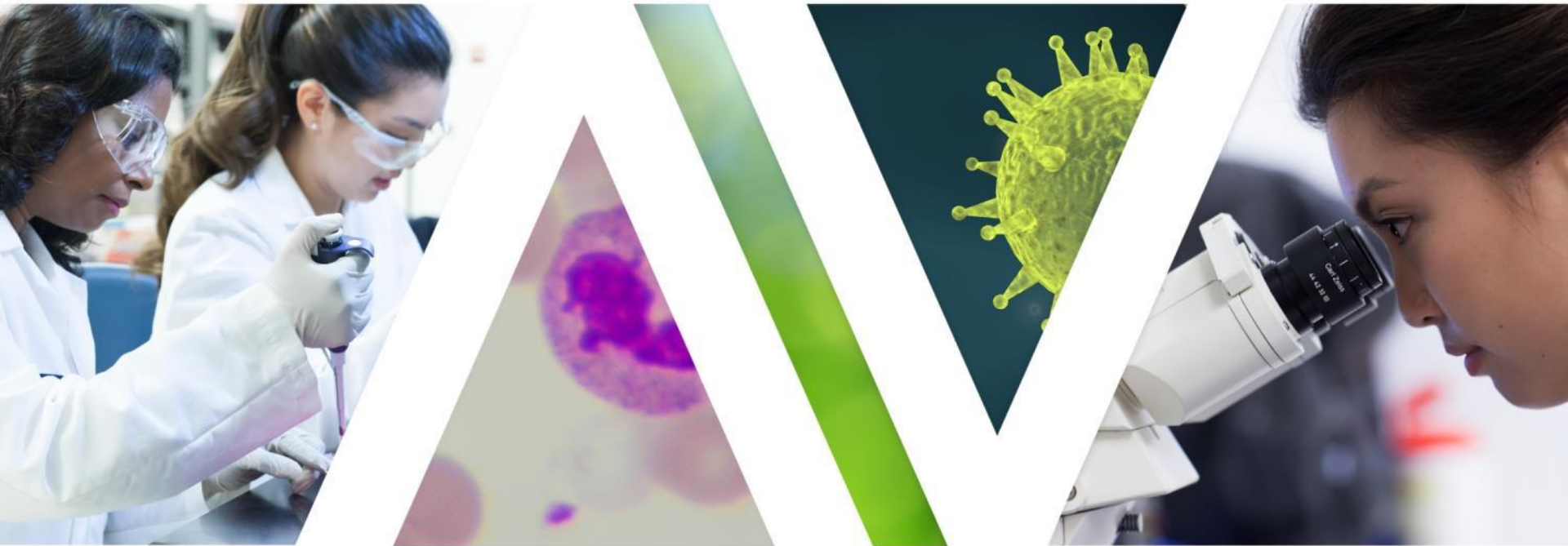


DYNAVAX

INNOVATING IMMUNOLOGY



Hepatitis B: Looking to the Future

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Overview

- Hepatitis B disease overview
- Current vaccination recommendations and uptake
- Overview of current vaccination options
- TLR-9 biology and application to vaccines
- Investigational vaccine HBsAg-1018 (HEPLISAV-B™) status update

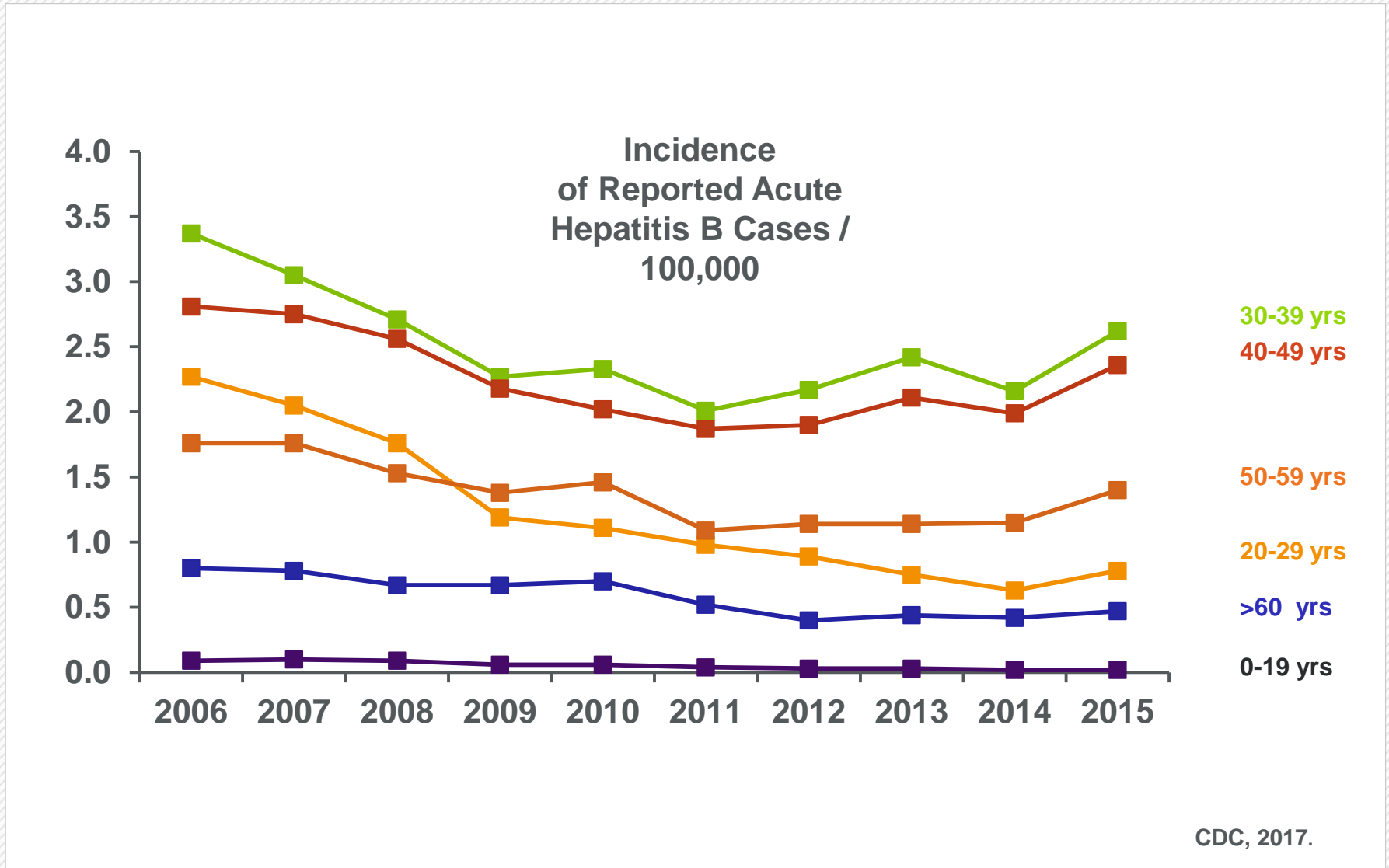
Hepatitis B Infection Continues Despite Vaccine Availability

- In the United States:
 - 5% of the population are infected with HBV¹
 - ~2.2 million manifest chronic hepatitis B infection^{2,3}
 - Up to 20,000 new documented hepatitis B infections are identified annually⁴
 - 5,000 deaths annually¹
- HBV is 100 times more infectious than HIV⁵
- 11 states account for 75.5% of the chronic HBV cases reported through NNDSS in 2014 (CA, FL, IL, MD, MI, MO, NC, NJ, NY, PA, TN)⁶

HIV, human immunodeficiency virus; NNDSS, National Notifiable Disease Surveillance System.

1. Centers for Disease Control and Prevention. Hepatitis B. In: *Epidemiology and Prevention of Vaccine-Preventable Diseases*. Hamborsky J, Kroger A, Wolfe S, eds. 13th ed. Washington, DC: Public Health Foundation. 2015.
2. Kowdley KV, Wang CC, Welch S, Roberts H, Brosgart CL. *Hepatology* 2012;56:422-33.
3. Gish RG, et al. *Hepatology* 2015;62:1339-41.
4. Centers for Disease Control and Prevention (CDC). Viral Hepatitis Surveillance United States, 2013. Available at: <http://www.cdc.gov/hepatitis/statistics/2013surveillance/pdfs/2013hepsurveillancerpt.pdf>
5. Centers for Disease Control and Prevention (CDC). Viral Hepatitis – Hepatitis B Information, 2015. Available at: <http://www.cdc.gov/hepatitis/hbv/bfaq.htm>
6. Centers for Disease Control and Prevention (CDC). Surveillance for Viral Hepatitis – United States, 2014. Available at: <http://www.cdc.gov/hepatitis/statistics/2014surveillance/commentary.htm#hepatitisB>

Significant Need for Hepatitis B Protection in Adults



Hepatitis B Continues to Negatively Impact Health

- Chronic hepatitis B (CHB) is a “silent epidemic”
- Most chronically infected people are asymptomatic^{1–3}
- CHB dramatically increases morbidity and mortality^{1–5}
 - People with chronic HBV are at a 12- to 300-times higher risk of liver cancer (HCC)¹
 - In the US
 - ~ 1,000 to 1,500 people die each year of HBV related HCC⁵
 - ~ 3,000 to 4,000 people die of hepatitis B-related cirrhosis⁵
- WHO recommends the inclusion of hepatitis B vaccine in immunization programs of all countries⁵
 - In 2011, 179 countries (of 193) had infant immunization programs⁶

HCC, hepatocellular carcinoma; WHO, World Health Organization.

1. Centers for Disease Control and Prevention. Hepatitis B. In: *Epidemiology and Prevention of Vaccine-Preventable Diseases*. Hamborsky J, Kroger A, Wolfe S, eds. 13th ed. Washington, DC: Public Health Foundation. 2015.
2. Centers for Disease Control and Prevention Division of Viral Hepatitis. *Division of Viral Hepatitis (DVH) Strategic Plan, 2016-2020: Bringing Together Science and Public Health Practice for the Elimination of Viral Hepatitis*. 2016. Available at: <http://www.cdc.gov/hepatitis/pdfs/dvh-strategicplan2016-2020.pdf>
3. Institute of Medicine. *Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C*. Washington, DC: The National Academies Press, 2010. Available at: <https://www.cdc.gov/hepatitis/pdfs/iom-hepatitisandlivercancerreport.pdf>.
4. National Academies of Sciences, Engineering, and Medicine. *Eliminating the Public Health Problem of Hepatitis B and C in the United States: Phase One Report*. Washington, DC: The National Academies Press, 2016. Available at: <http://www.nap.edu/catalog/23407/eliminating-the-public-health-problem-of-hepatitis-b-and-c-in-the-united-states>
5. World Health Organization. Emergencies, preparedness, response: Hepatitis B. 2016. Available at: <http://www.who.int/csr/disease/hepatitis/whocdscsrlyo20022/en/index1.html>.
6. Plotkin S, Orenstein W, Offit PA, eds. *Vaccines*. 6th ed. Elsevier; Philadelphia, Penn. 2012:205-34.

ACIP Recommendations for Hepatitis B Vaccination In Adults

Immunization of Adults

- Hepatitis B vaccination is recommended for all unvaccinated adults at risk for HBV infection
 - Persons at risk for infection by sexual exposure
 - Persons at risk for infection by percutaneous or mucosal exposure to blood
 - Others
 - International travelers to regions with high or intermediate levels (HBsAg prevalence of >2%) of endemic HBV infection
 - Persons with chronic liver disease
 - Persons with HIV infection
 - All adults requesting protection from HBV infection

Adults With Diabetes Mellitus (DM)

- Unvaccinated adults with DM who are aged 19–59 years
- Unvaccinated adults with DM who are aged ≥60 years, at the discretion of the treating clinician

1. Mast EE, et al; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). *MMWR Recomm Rep.* 2006;55(RR-16):1-33. 2. Sawyer MH, et al. Centers for Disease Control and Prevention (CDC). Use of hepatitis B vaccination for adults with diabetes mellitus: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morb Mortal Wkly Rep.* 2011;60:1709-1711.

Despite the ACIP Recommendations...

- Little shift in HBV vaccination rates among adults who have diabetes
 - Among US adults with diabetes, only **23.5%** of those aged 19–59 years and **13.5%** of those aged ≥ 60 years have been vaccinated against HBV¹ (vaccination for people with diabetes ≥ 60 years is at healthcare provider's discretion)

1. Williams WW, et al. *MMWR Surveill Summ.* 2016;65:1-36.

FDA-Approved Adult Hepatitis B Vaccines

Products	Dose	Schedule (Months)
Engerix-B [®] (GSK)	20 µg rHBsAg 500 µg alum	0, 1, 6
Recombivax HB [®] (Merck)	10 µg rHBsAg 500 µg alum	0, 1, 6
Twinrix [®] (GSK)	720 ELISA units hep A 20 µg rHBsAg 450 µg alum	0, 1, 6

ELISA, enzyme-linked immunosorbent assay; hep, hepatitis; rHBsAg, recombinant hepatitis B surface antigen.

Adult Hepatitis B Vaccination

Room for Improvement

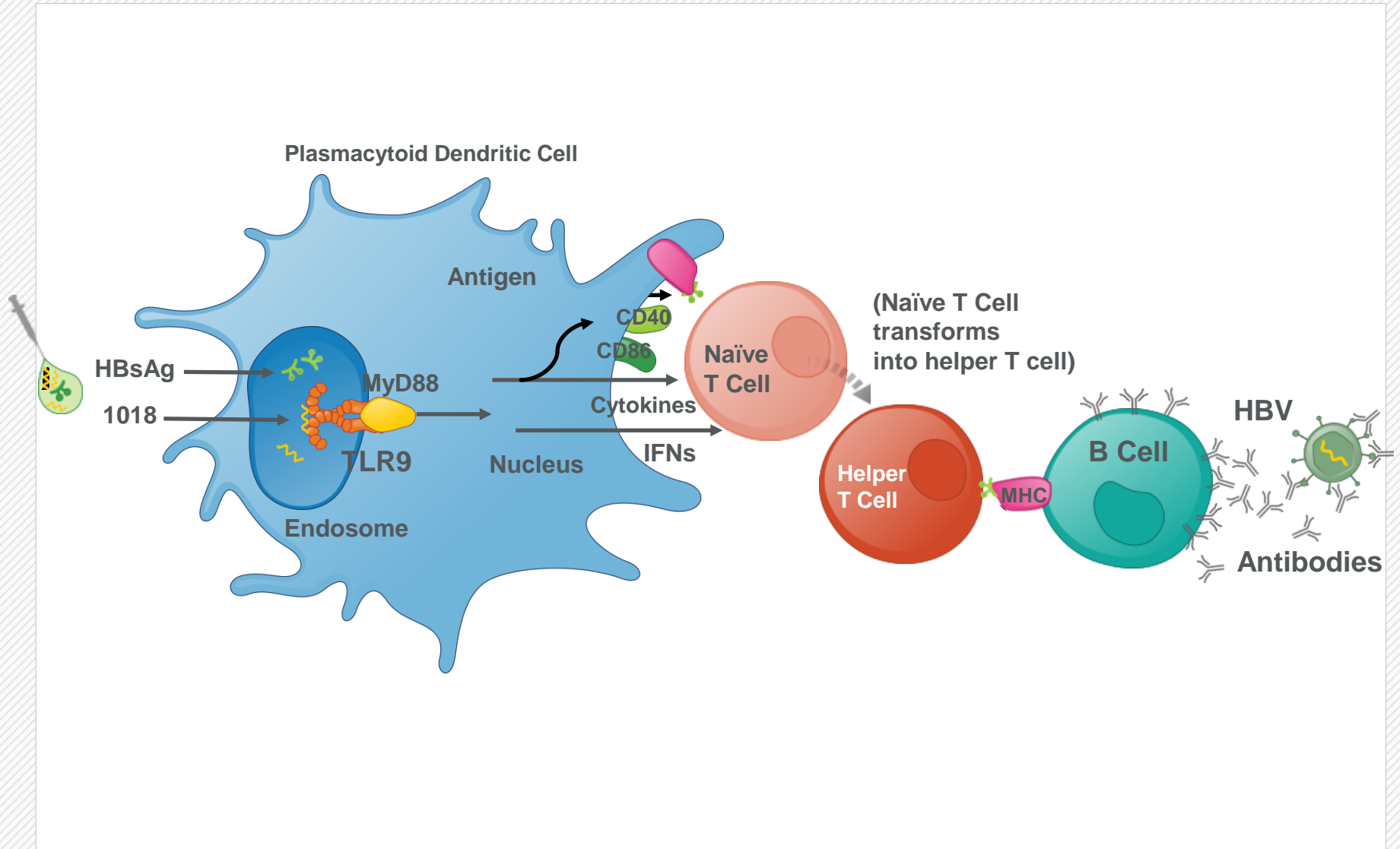
- **Rate of Protection**
 - Currently marketed vaccines provide lower rate of protection for significant segments of those at risk of infection
- **Time to Protection**
 - Current 3 dose regimen over 6 months leaves patients exposed to infection
- **Compliance**

In VSD study, of 88,711 adults ⁽¹⁾		In STD clinic in San Diego, CA, of 3,538 MSM ⁽²⁾ using accelerated schedule 0, 1, 4 months	
81%	Received 2 doses 8 years	64%	Received 2 doses 5 years
54%	Completed series in 1 year	43%	Completed series in 5 years

¹ Compliance With Multiple-Dose Vaccine Schedules Among Older Children, Adolescents, and Adults: Results From a Vaccine Safety Datalink Study. American Journal of Public Health 2009; 99(2):389-397

² The Adult Hepatitis Vaccine Project – California, 2007-2008. Morbidity Mortality Weekly Report 2010;59(17);514-516 Hepatitis B Vaccination Among High-Risk Adolescents and Adults – San Diego, California, 1998-2001. Morbidity Mortality Weekly Report 2010; 51(28);618-621 Hepatitis B Vaccination in Six STD Clinics in the US Committed to Integrating Viral Hepatitis Prevention Services. Public Health Rep 2007; 122: 42-47

1018 Adjuvant Targets Innate Immune System for Development of Anti-HBs



Investigational Vaccine HBsAg-1018 (HEPLISAV-B™)

- **Antigen:** Contains 20 µg rHBsAg
- **Adjuvant:** Contains 3,000 µg 1018
 - Adjuvant (CpG oligonucleotide)
 - Short, single-stranded oligonucleotide with unmethylated CpG motifs
 - Toll-like receptor-9 (TLR-9) agonist
 - Mimics natural response to infection
- 2 doses on 0, 1 month schedule
- Proposed indication under FDA review: 18 years of age and older
- PDUFA action date: 09 November 2017

CpG, 5'—C—phosphate—G—3'; FDA, Food and Drug Administration; HBsAg, hepatitis B surface antigen; PDUFA, Prescription Drug User Fee Act; VRBPAC, Vaccines and Related Biological Products Advisory Committee.

Conclusion

Q & A