Hepatitis B vaccination worldwide: Lessons learnt and the way forward

VHPB Russia meeting

Oct 2018

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History

- Hepatitis B vaccines have been available since early 1980's
- First recommended in industrialized countries for high risk groups (MSM, IDU, multiple sex partners)
- In 1991, the Global Advisory Group of EPI (Expanded Programme on Immunization) set 1997 as the target for integrating the hepatitis B vaccination into **national immunization programmes worldwide**. Adherence by WHO and WHA (resolution 45.17) in 1992

History (2)

- In 2010, Member States re-iterated the 1992 resolution and adopted resolution 63.18, which called WHO to draft a comprehensive **viral hepatitis prevention and control strategy,** including **universal hepatitis B immunization** programmes and development of **time-specific immunization goals**

FEATURES OF HEPATITIS B VACCINE

- Available since 1982 (plasma); 1986 (recombinant); recent Third generation vaccines: mammalian cell derived recombinant vaccines (HBsAg/ S, preS1, preS2 antigens), with enhanced immunogenicity – other under development
- Monovalent or in combination with other vaccines
- Schedule is flexible
- High immunogenicity (three dose, 95-99%)
- Long-term protection
  - Antibody concentration declines over time, but clinically significant breakthrough infections are rare (> 30 years of follow up)
  - Immunological memory for HBsAg can outlast the antibody detection providing long-term protection
- Good safety profile

  "One of the most studied vaccines"

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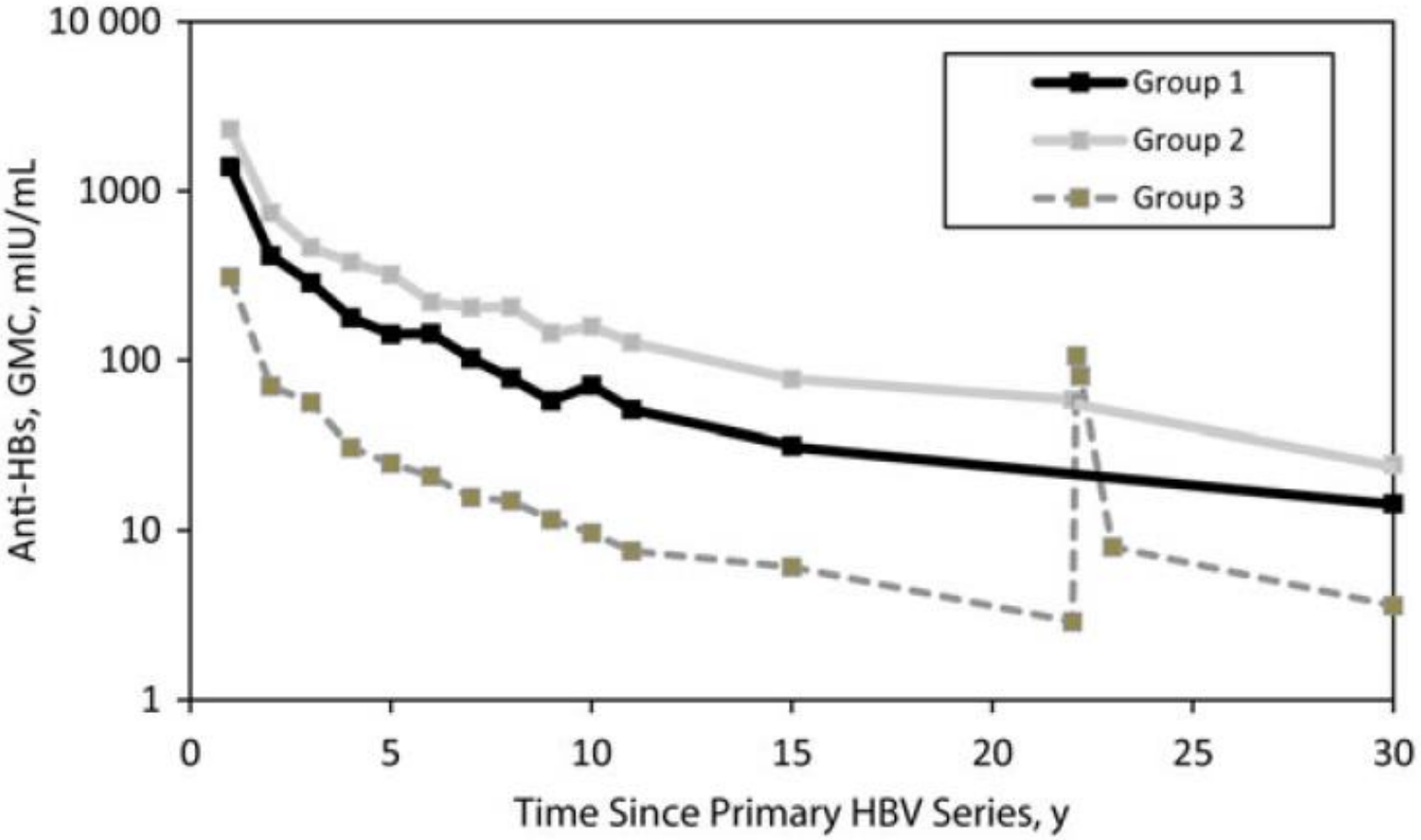
The Journal of Infectious Diseases

Antibody Levels and Protection after Hepatitis B Vaccine: Results of a 30 year Follow-up Study and Response to a Booster Dose

--Manuscript Draft--



Bruce et al, JID, 2016

Journal of Infectious Diseases Advance Access published January 21, 2016

The Journal of Infectious Diseases

EDITORIAL COMMENTARY

Long-term Protection After Hepatitis B Vaccine

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for the first time results of a 30-year follow-up study and response to a booster dose in an Alaskan Native population. It is the longest cohort study on extended protection after hepatitis B vaccination to date. Their unique data add a new piece of evidence to the puzzle of long-term immunity: no significant breakthrough infections were diagnosed in the vaccinees during the 30-year period, and 51% (125 of 243) still had anti-HBs levels ≥10 mIU/mL 30 years after initial vaccine administration [10]. Initial anti-HBs level and age at vaccination seemed to play an important role in the persistence of antibodies.

To illustrate the prolonged duration of protection and immune memory against hepatitis B, Bruce and colleagues [10] offered participants with anti-HBs levels <10 mIU/mL a challenge hepatitis B vaccine dose 30 years after primary vaccination. An anamnestic response of 88% was measured 30 days after challenge. These

induced antibodies. The data presented by Bruce et al confirm statements from the World Health Organization, Centers for Disease Control and Prevention, and Viral Hepatitis Prevention Board that booster vaccination against hepatitis B for immunocompetent children and adults is not recommended [22–24]. The absence

GOOD SAFETY PROFILE

- More than **1,000,000** people studied in the **clinical trials**
- 30% of adults and < 10% of children have sore arm and/or local induration
- one of the safest vaccines ever developed
- **> 2,500 million** doses used world wide since 1982
- Pain and tenderness in 15% (3%-29%) of vaccinations, fever > 37.7°C in 1%-6%, erythema, swelling and headache 3%
- Fewer reactions in children
  - Fever, headache, muscle aches, nausea, vomiting, loss of appetite, and fatigue occur at same rate as in placebo

Ref: see also Esposito et al. Clin Mircobiol & Inf - 2014

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WHO RECOMMENDATION –JULY 2017

WHO Position
Vaccination Schedule

- 3-dose schedule: monovalent birth dose, second and third doses given with first and third doses of DTP vaccine
- OR 4-dose schedule: monovalent birth dose, following 3 doses given with other routine infant vaccines
- At least 4 weeks between doses
- No evidence to support need for booster dose
- Catch-up vaccination should be considered based on available resources. Priority should be given to younger age groups

World Health Organization

Hepatitis B vaccines: WHO position paper, July 2017
http://www.who.int/immunization/documents/positionpapers/en/

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schedules

- 0,1,6 or 0,1,2,12 month schedule
- End result is equal
- Minimal 4 weeks between 2 primary injections
- Minimal 4 months between last and first dose (in 3 dose schedule)
  - Shortest schedule: 0,1,4 month
- Schedule is very flexible
  - Adaptation to all existing infant immunization programmes
  - As many schedules as countries/regions
- 2 dose-schedule: 0-6 months (adult dose for ado's)

WHO RECOMMENDATION –JULY 2017

WHO Position
Special Populations

- Vaccination of groups at highest risk of acquiring HBV infection is recommended:
  - Patients who frequently require blood/blood products, dialysis or diabetes patients, recipients of solid organ transplants, persons with chronic liver disease or HIV, persons interned in prisons, persons who use injecting drugs, household and sexual contacts of persons with chronic HBV infection, men who have sex with men, persons with multiple sexual partners, healthcare workers and others who may be exposed to potentially infectious body fluids during their work
  - HIV-positive individuals should be vaccinated as early as possible in the course of HIV infection.
  - Immunocompromised individuals may have reduced immune response following vaccination.

World Health Organization

Hepatitis B vaccines: WHO position paper, July 2017
http://www.who.int/immunization/documents/positionpapers/en/

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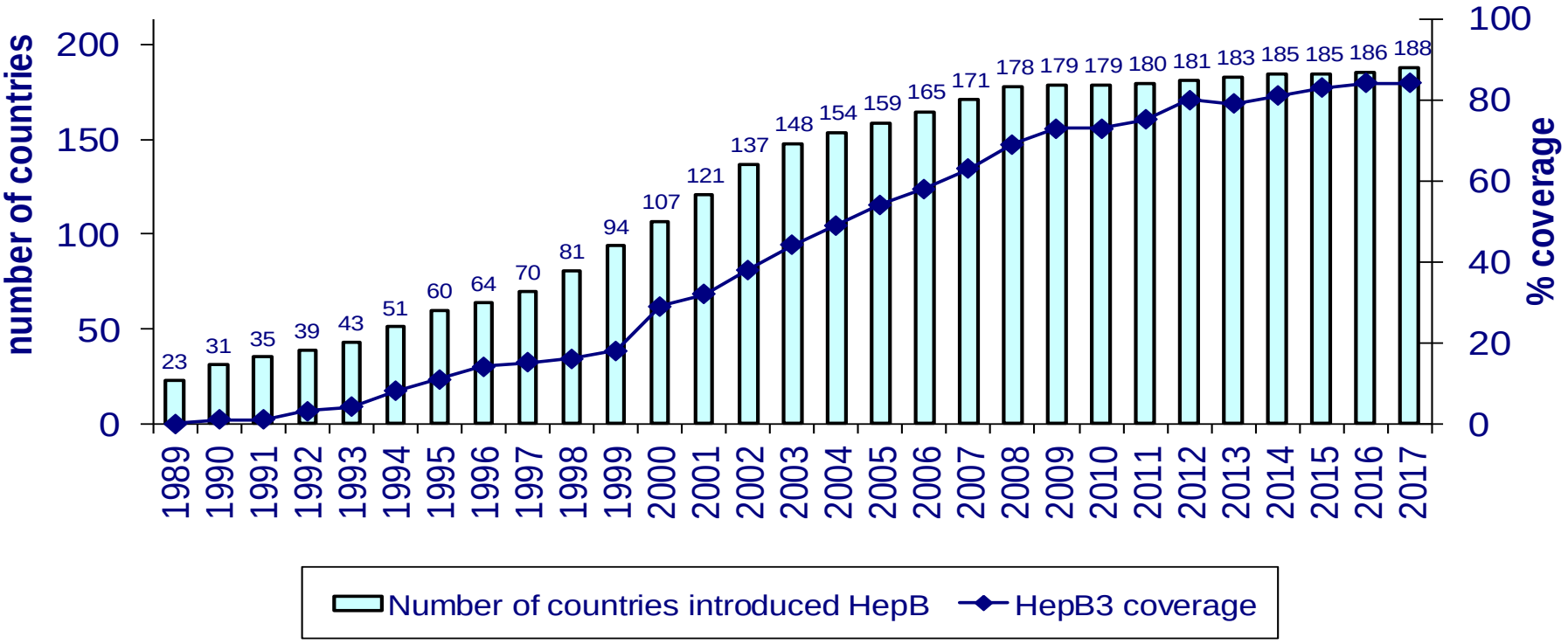
NUMBER OF COUNTRIES HAVING INTRODUCED HEPATITIS B VACCINE AND GLOBAL INFANT COVERAGE FOR HEPATITIS B 3RD DOSE (HEPB3), 1989-2017



Source: WHO/UNICEF coverage estimates 2017 revision, July 2018, and WHO database as at 06 July 2018. Immunization Vaccines and Biologicals, (IVB), World Health Organization. 194 WHO Member States. Date of slide: 15 July 2018.

2017: excluding 3 countries where HepB administered for adolescents

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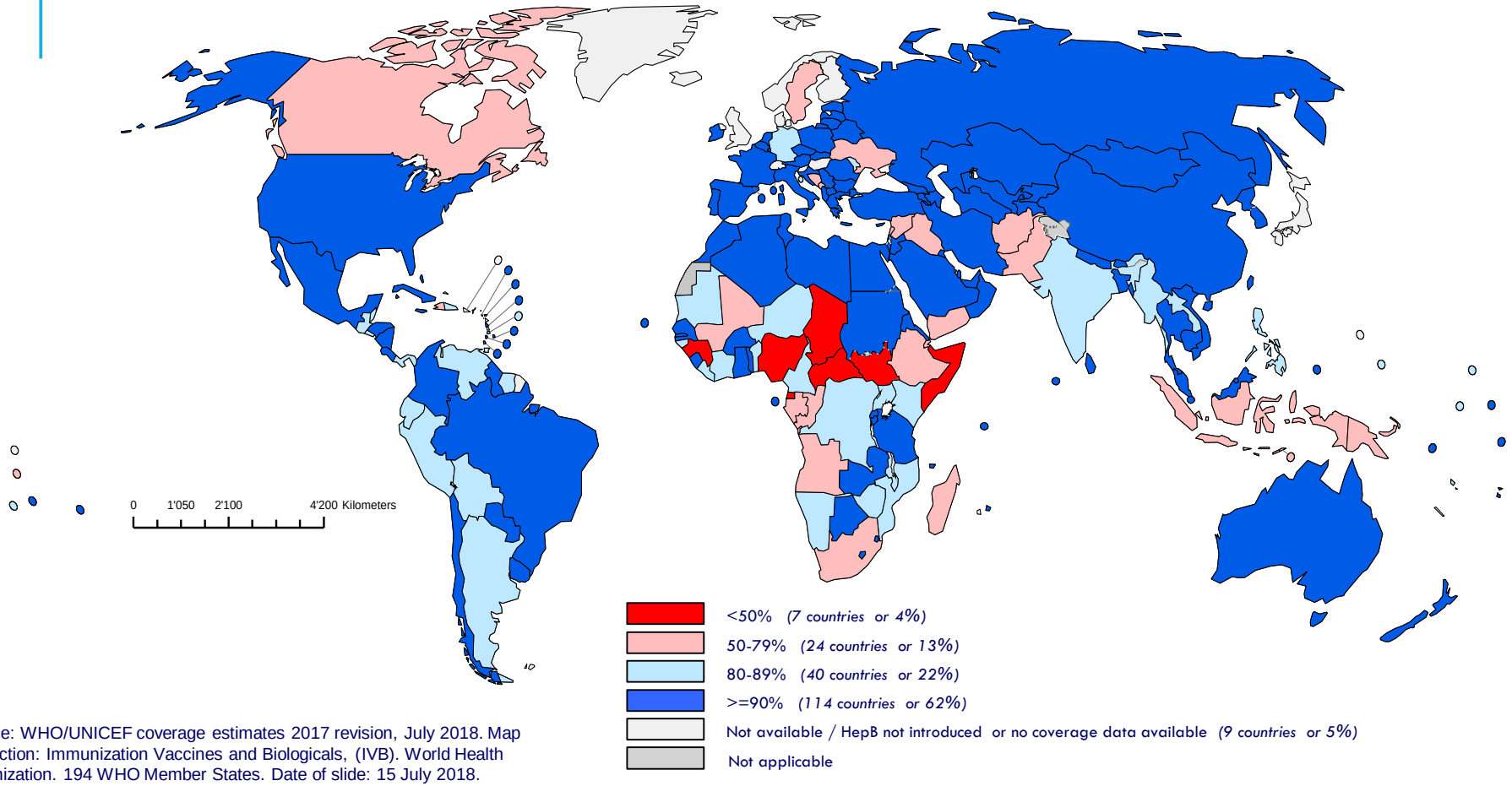
IMMUNIZATION COVERAGE WITH HEPB3 IN INFANTS, 2017



Source: WHO/UNICEF coverage estimates 2017 revision, July 2018. Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization. 194 WHO Member States. Date of slide: 15 July 2018.

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3-DOSE HEPATITIS B VACCINE: 84% COVERAGE: IMPACT ON INCIDENCE

HBV

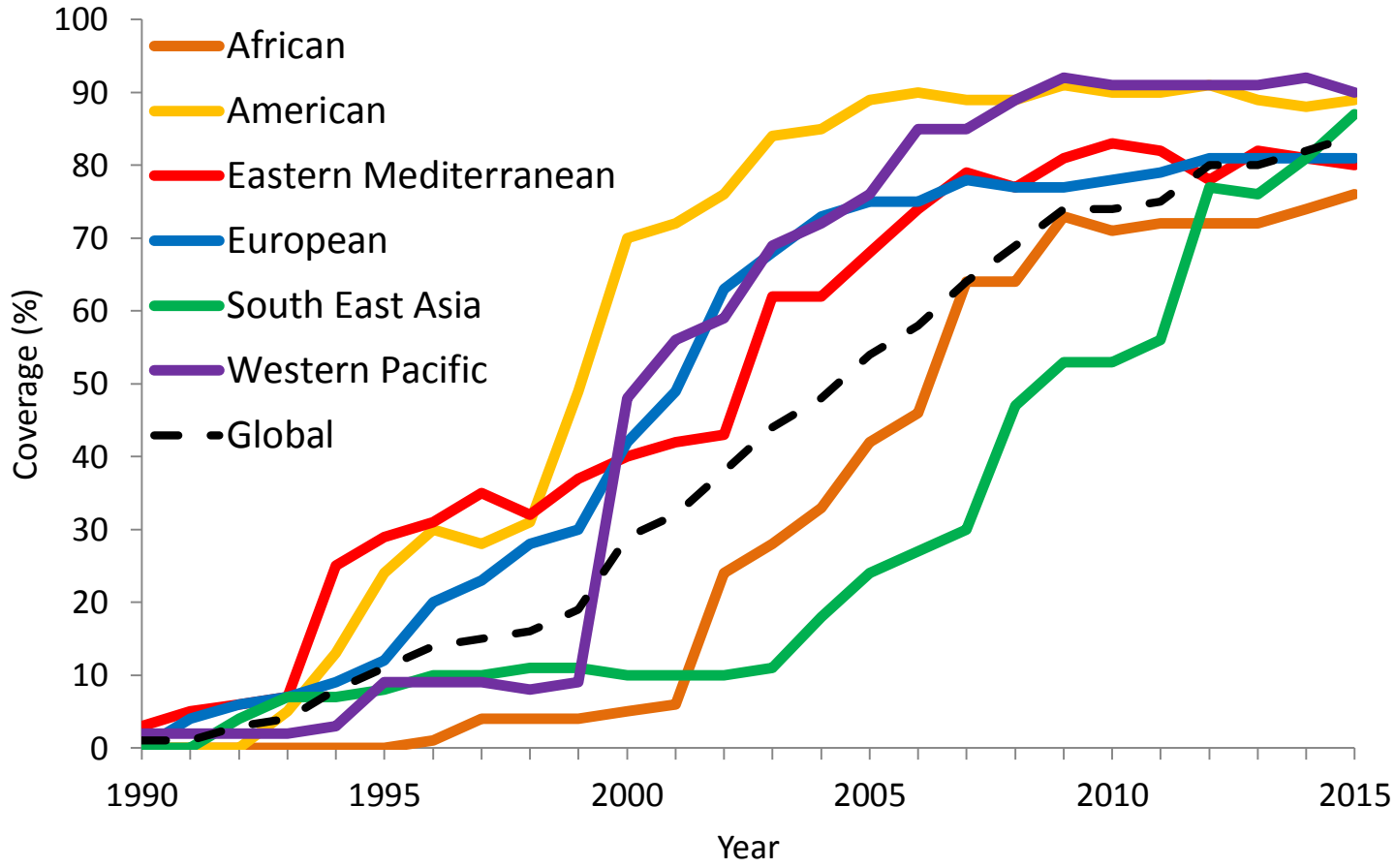

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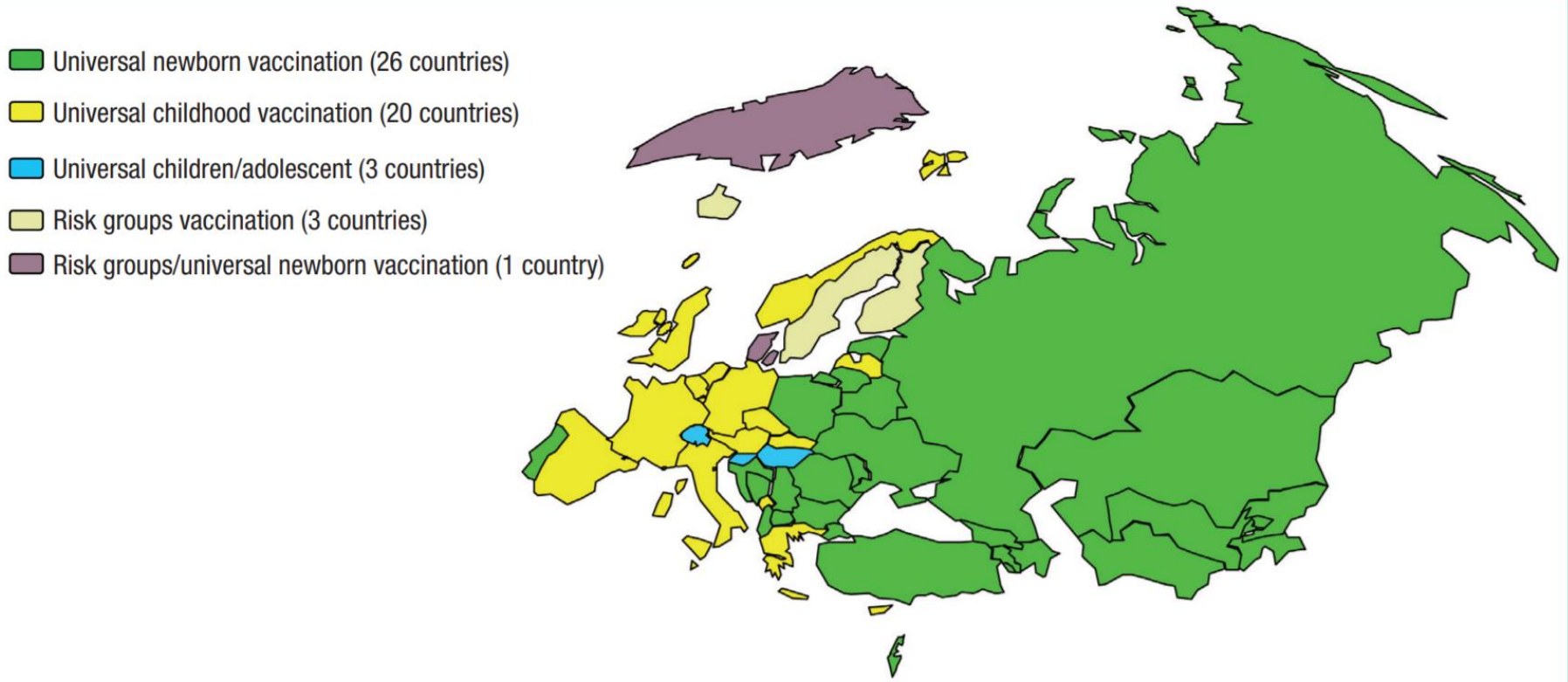
Fig. 1. Hepatitis B immunization policy, WHO European Region 2017



Source: WHO/UNICEF joint reporting forms.

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IS THERE AN IMPACT AFTER ALL THIS YEARS OF HEPATITIS B VACCINATION

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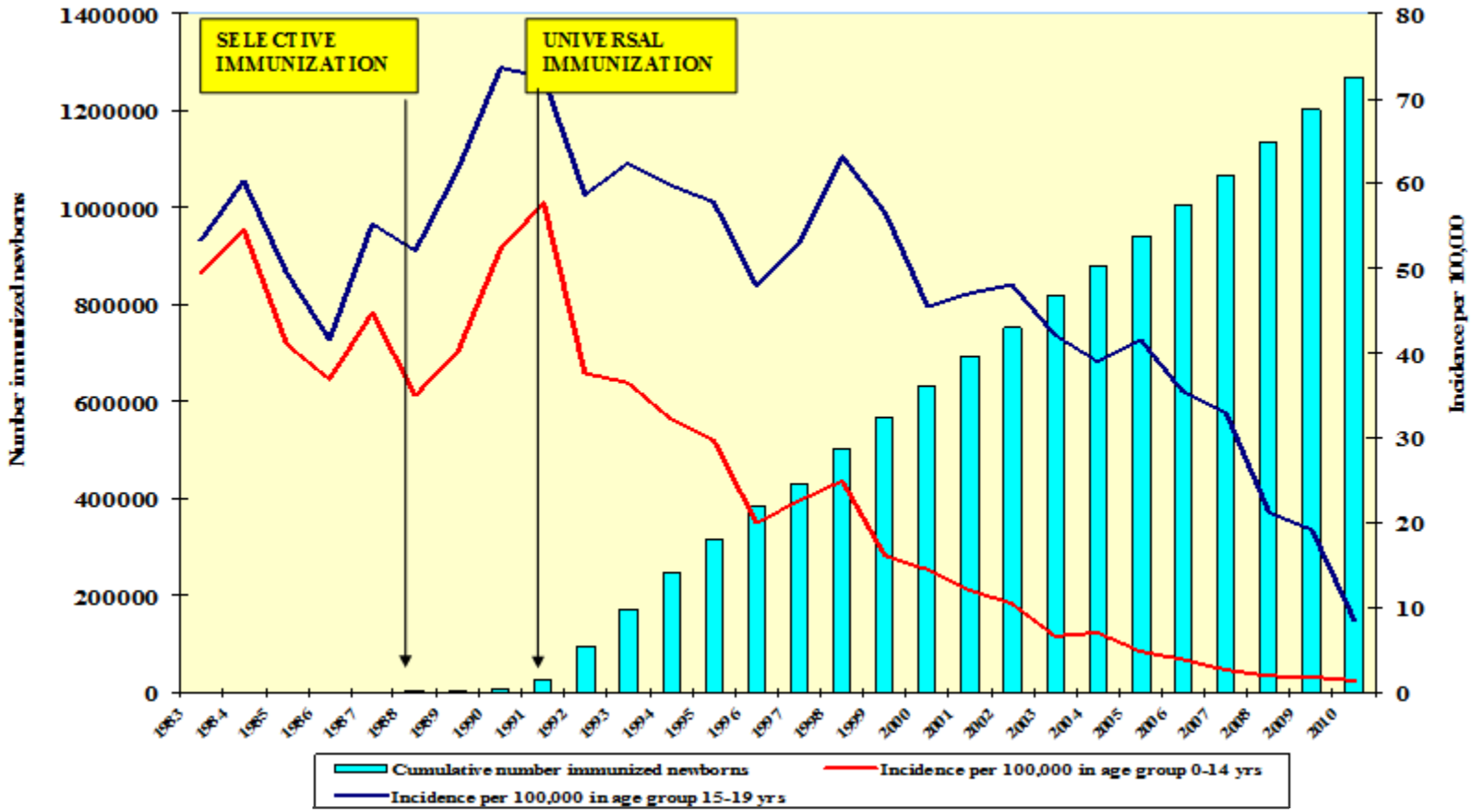
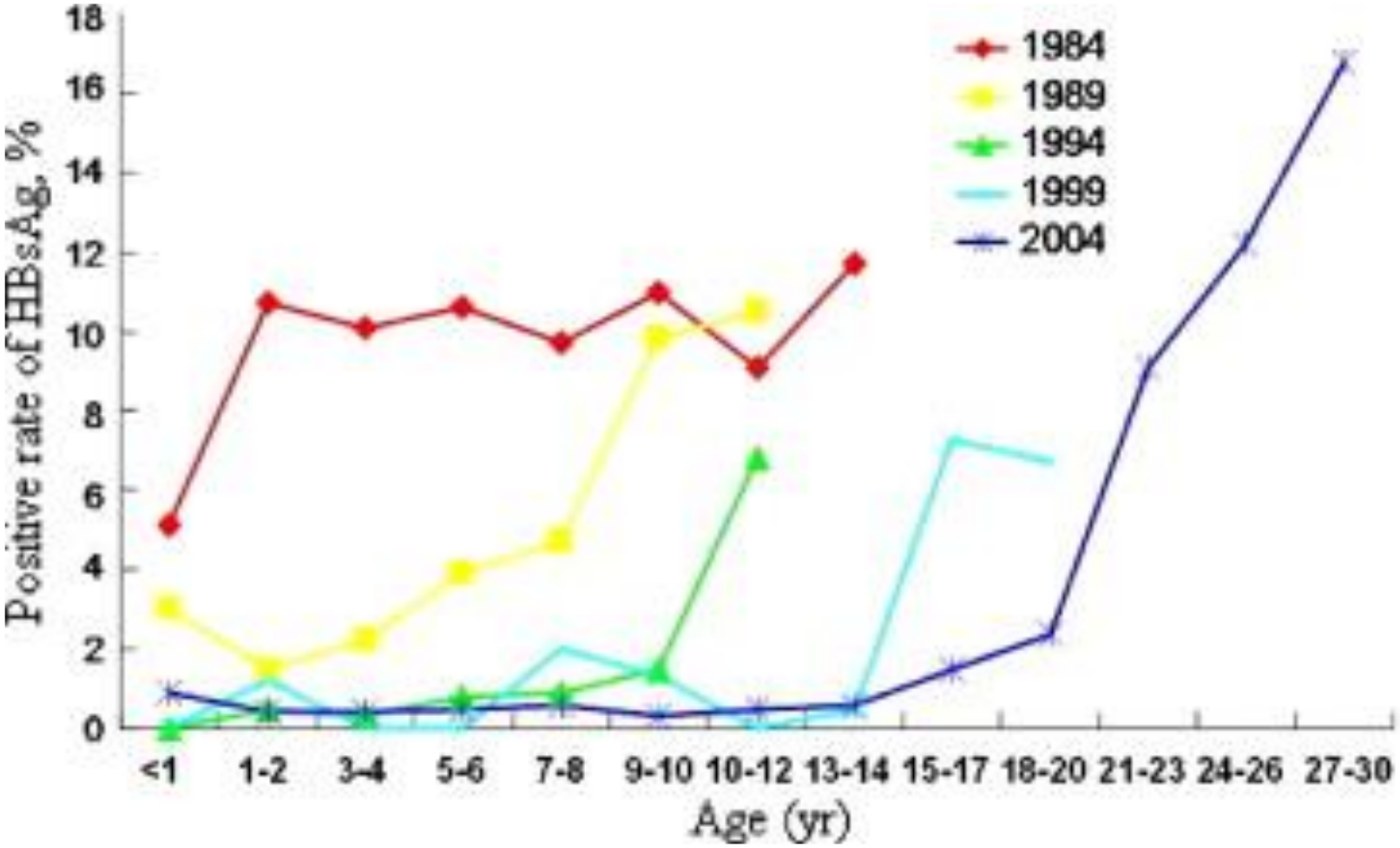
Example of Bulgaria

Cumulative number of newborns immunized with HBV vaccine and hepatitis B incidence (per 100,000) in children and young adults, Bulgaria, 1983-2010



Source: National Centre of Infectious and Parasitic Diseases, Bulgaria



Prevalence of hepatitis B surface antigen (HBsAg) in healthy children in Taipei from 1984 to 2004. The mass hepatitis B vaccination started in 1984.

From D.-S. Chen; Journal of Hepatology, 2009

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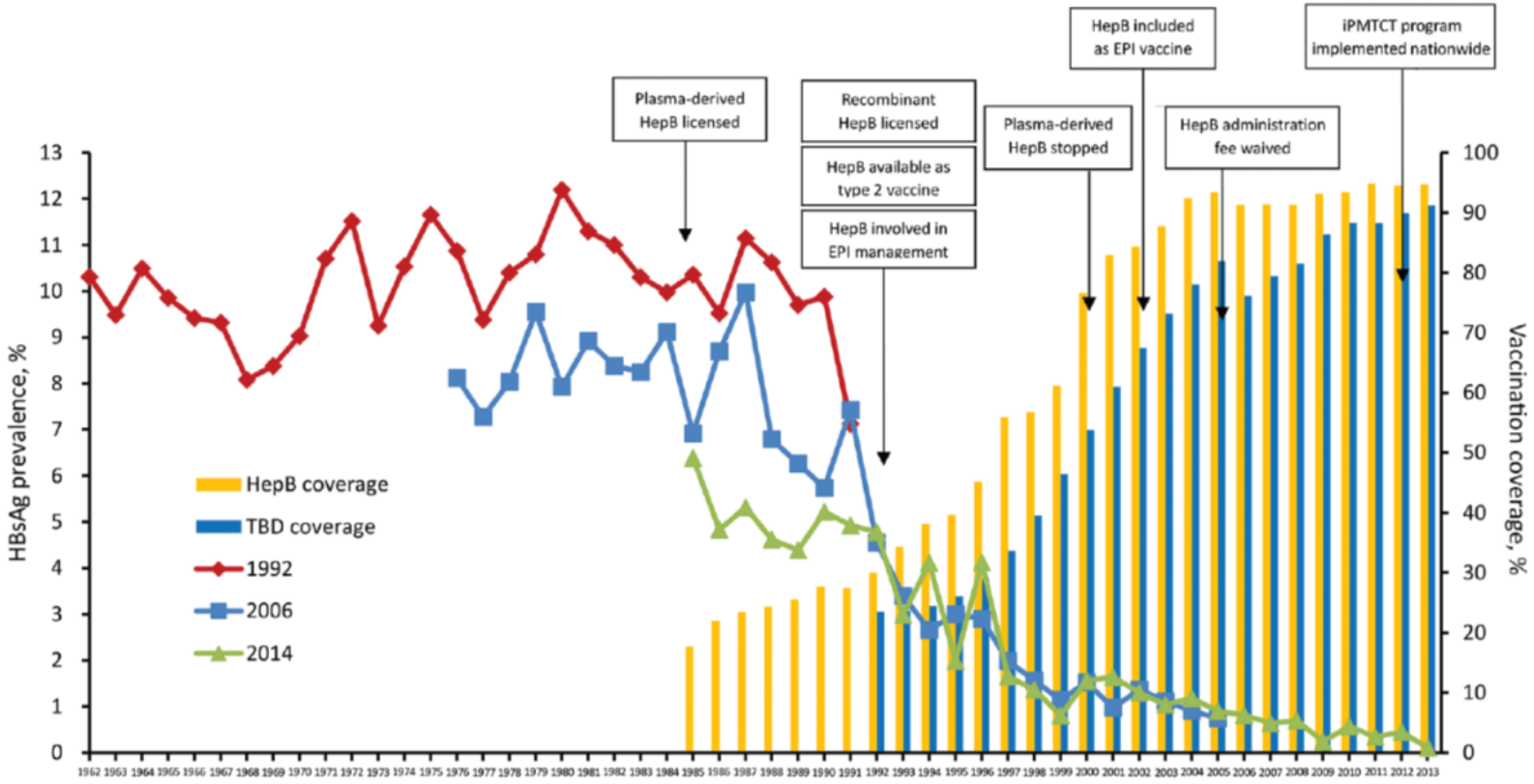
CONTROL OF HBV INFECTION THROUGH VACCINATION INCLUDING TIMELY BIRTH DOSE, CHINA, 1962-2013 BIRTH COHORTS



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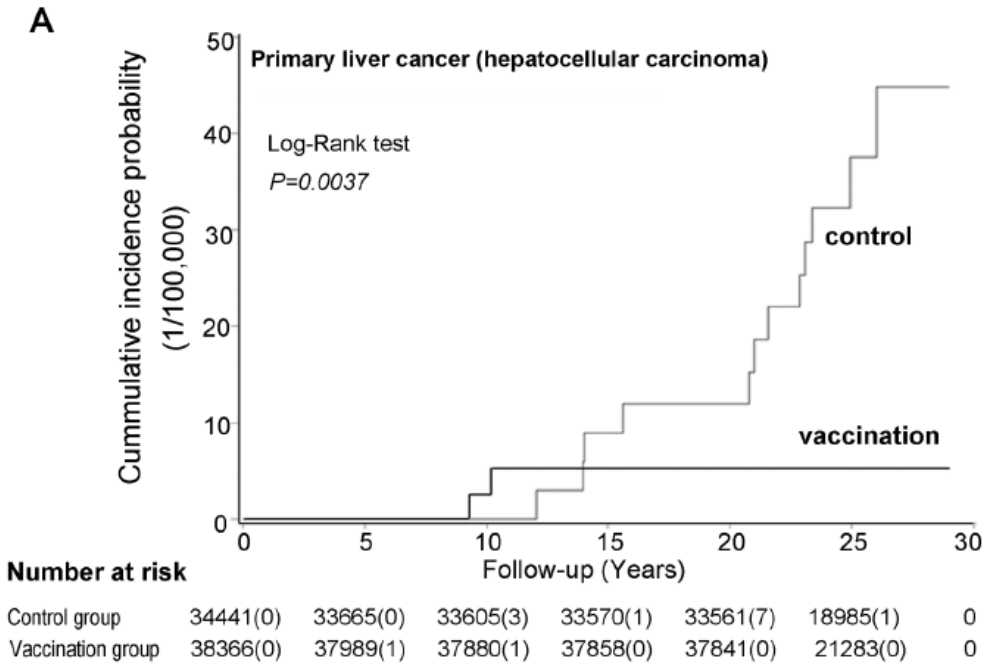

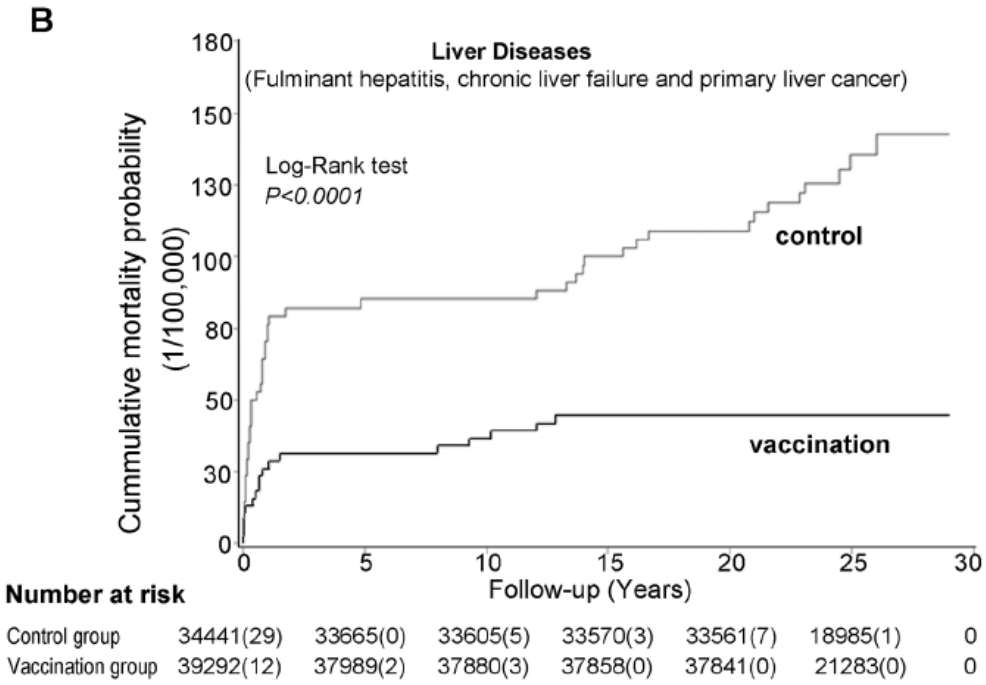

CHINA, QIDONG,
CROSS SECTIONAL SURVEYS IN 1996-2000 AND 2008-2012: INCIDENCE OF PLC AND MORTALITY OF END STAGE LIVER DISEASE SIGNIFICANTLY LOWER IN VACCINEES VERSUS CONTROLS

CHUNFENG QU, PLOS MEDICINE, 2014

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DO WE STILL NEED TO TALK ABOUT HBV VACCINATION

- Despite the availability of safe and effective HBV vaccines since more than 35 years
- Global burden of disease is still substantial

STATUS OF HEPATITIS B, 2017

Despite the availability of safe and effective HBV vaccines since more than 35 years

Global burden of disease is still substantial:

- About 2000 million (2 billion) have been infected
- 240 - 350 million chronically HBV infected,
- ~600,000 deaths/yr as a result of HBV infection
- 57% of cirrhosis was attributable to either HBV or HCV
  - 30% of cirrhosis was attributable to HBV
- 78% of HCC was attributable to HBV or HCV
  - 53% of HCC was attributable to HBV

Ref: J.F. Perz et al. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. Journal of Hepatology 45 (2006) 529–538.

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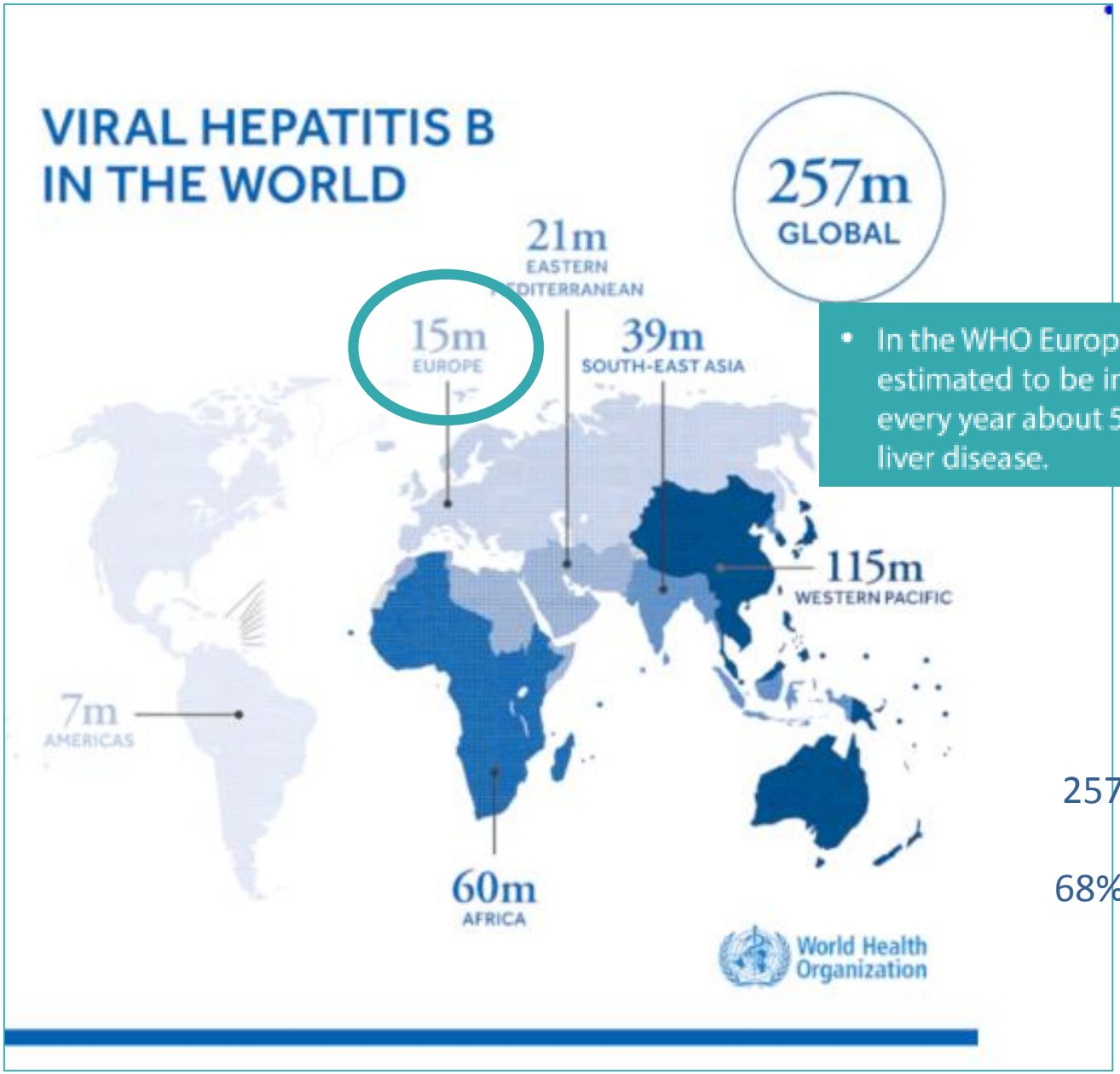

- In the WHO European Region, 15 million people are estimated to be infected with hepatitis B virus and every year about 56 000 die from hepatitis B-related liver disease.

Prevalence:
257 million people living with HBV
68% in Africa /Western Pacific

Global hepatitis report infographics http://www.who.int/hepatitis/news-events/global-hepatitis-report2017-infographic/en/

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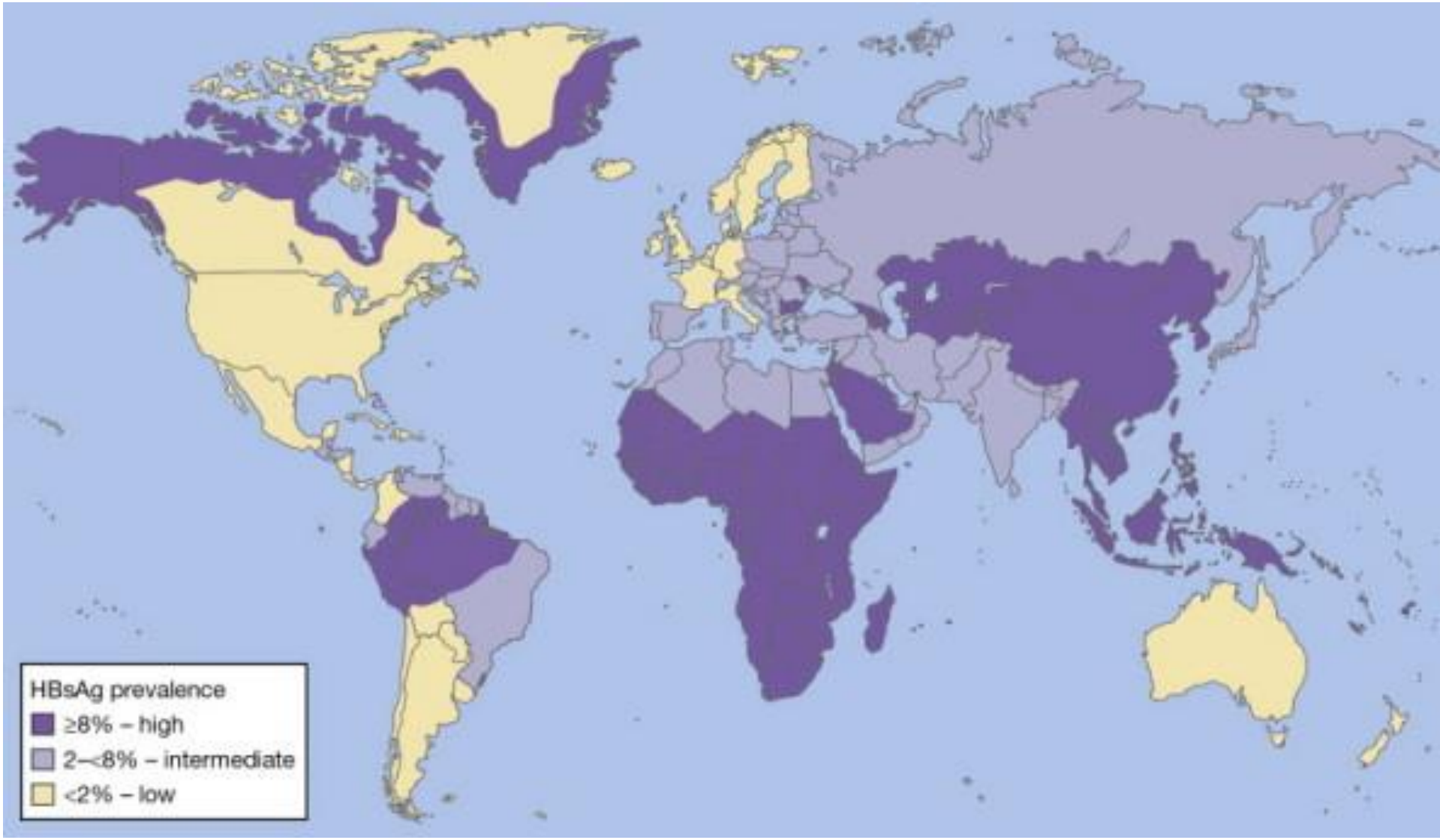
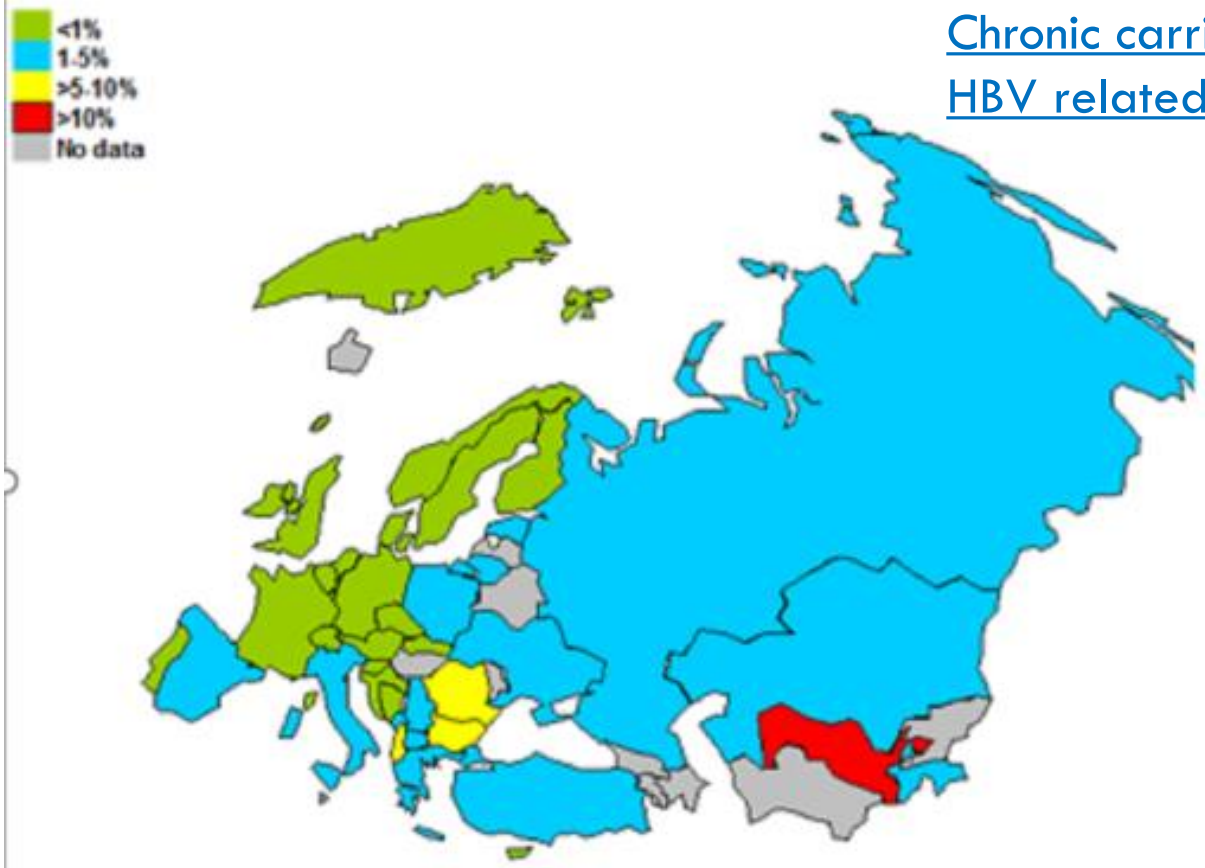


Plotkin et al – Vaccines 6th Edition - 2017

ENDEMICITY OF HEPATITIS B IN EUROPE (WHO EURO) - 2013

Chronic carriers in Euro: 15 million people

HBV related mortality: 56 000



Estimated prevalence of carriage of hepatitis B surface antigen, WHO European Region, 2013.

http://www.euro.who.int/en/health-topics/communicable-diseases/hepatitis/data-and-statistics/fact-sheet-hepatitis-b

WHO - GLOBAL HEALTH SECTOR STRATEGY ON VIRAL HEPATITIS

Goal: eliminate viral hepatitis as major public health threat by 2030

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WHAT ARE THE CHALLENGES FOR HBV VACCINATION

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TREMENDOUS PROGRESS SINCE 1990

Hepatitis B

1% Global coverage of infants in with three doses of hepatitis B vaccine in **1990**

81% Global coverage of infants in with three doses of hepatitis B vaccine in **2013**

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BUT THE WORK IS NOT FINISHED

- Increasing number of **immigrants from mid and high endemic** countries moving to Europe, leading to changes in hepatitis B epidemiology of low endemic countries → surveillance !
- Transmission is not **confined within the immigrant communities** but has been reported to spread horizontally or sexually beyond, creating new dynamics of infectious disease transmission[1]
- With availability of new drugs for treatment of hepatitis C, focus (and financial resources) is moving from prevention to treatment, with risk of decreasing vaccination coverage hepatitis B vaccination

1. Chu JJ, et al. Eur J Public Health (2012)

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CHALLENGES FOR THE FUTURE

- Keep or increase vaccination coverage

  Sustainability

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HEPATITIS B 3 VACCINE COVERAGE, 2015

KEEP the coverage

Coverage (%)	No of countries
≥ 95	24
94	8
91 - 93	5
80 – 90	6*
< 80	2**
Total:	45

Increase

* BiH, France, Germany, Montenegro, Romania, Slovenia

** San Marino, Ukraine

Source: WHO/UNICEF estimate

World Health Organization
REGIONAL OFFICE FOR Europe

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CHALLENGES FOR THE FUTURE

- Keep or increase vaccination coverage (sustainability)
- Universal vaccination <> Risk group vaccination

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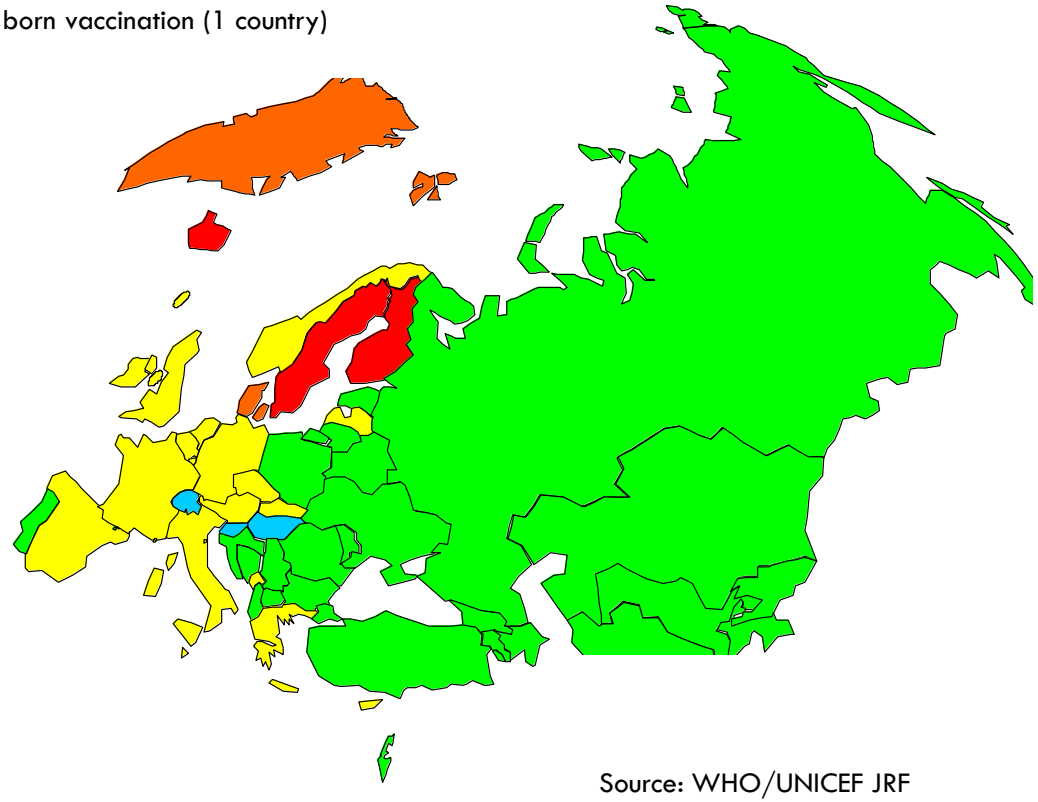
HEPATITIS B IMMUNIZATION POLICY, WHO EUROPEAN REGION

Universal newborn vaccination (26 countries)
Universal childhood vaccination (20 countries)
Universal children/adolescents (3 countries)
Risk groups vaccination (3 countries)
Risk groups / universal new born vaccination (1 country)



Source: WHO/UNICEF JRF

World Health Organization
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Hepatitis B vaccination policy

Risk group approach versus universal vaccination

Risk group vaccination	Universal vaccination
• Individual risk perspective • Difficulty of accessing high risk groups • No identifiable risk among 50% of acute HBV patients in industrialized countries • Infections often acquired before risk is recognized • Often low completed schedule coverage • Negative social stigma • So far, programmes targeting risk groups failed to eliminate HBV circulation	• Global approach • More easy to implement through existing structures and use of combination vaccines • Protection of future risk groups • Optimal coverage • Cost-effective in low to high endemic setting • Impact on HBV control and endemicity

Source: Van Damme et al. BMJ 2013;346:f4057

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HEPATITIS B VACCINATION POLICY

Ideally :

combination between

Universal and **Risk group** vaccination

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CHALLENGES FOR THE FUTURE

- Keep or increase vaccination coverage (sustainability)
- Universal vaccination – Risk group vaccination
- timely vaccination – birth dose

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STRATEGIC ADVISORY GROUP OF EXPERTS, 2016

SAGE reemphasized **the importance of the birth dose** and urged all countries to introduce the universal birth dose without further delay

All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours

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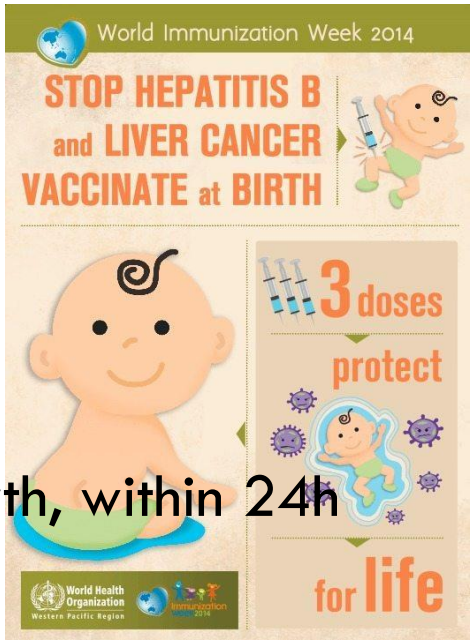
BIRTH DOSE



- Offer hepB vaccine as soon as possible after birth, within 24h
- As a monovalent vaccine
- If specific hepBIg available, simultaneous administration, at an other injection site
  - Adds 2-3% protective efficacy (97% vs. 95%)

The hepatitis B vaccine administered shortly after birth serves 2 functions: as post-exposure prophylaxis following exposure and as protection for future exposures

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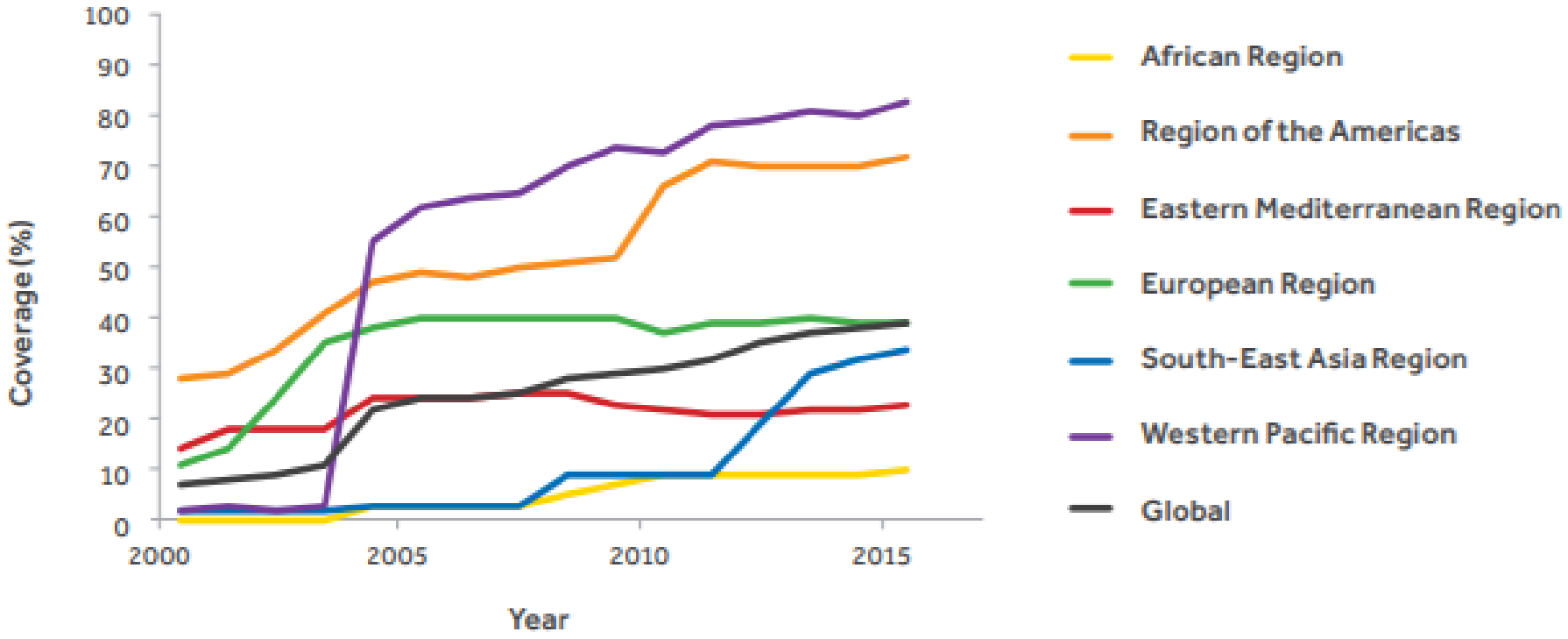
Fig. 5. Hepatitis B birth dose coverage, by WHO region, 2000–2015: good progress in the Region of the Americas and Western Pacific Region



Source: Joint UNICEF–WHO reporting form

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CHALLENGES FOR THE FUTURE

- Keep or increase vaccination coverage (sustainability)
- Universal vaccination – Risk group vaccination
- timely vaccination – birth dose
- Cope with vaccine issues and vaccine confidence

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LEARN FROM PAST TO COPE WITH THE FUTURE

In the past hepatitis B vaccination programmes were several times damaged by unsubstantiated rumors:

- Hepatitis B derived vaccine from plasma, linked with aids
- HepB can be sexually transmitted
- Safety concerns
  - HepB vaccine was Linked to Multiple Sclerosis, Autism, …
  - Picked up by anti-vaccine
  - Although no causal link with vaccine
  - communication of rational arguments did not seem to have impact

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A STUDY LINKING AUTISM TO CHILDHOOD VACCINATIONS HAS NOT ONLY BEEN DEBUNKED, BUT IT IS AN "ELABORATE FRAUD." WE TRUST THAT THIS ENDS THE MATTER.
LA LA LA!!
ANTI-VACCINE ACTIVISTS

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VACCINE HESITANCY: WE NEED TO BE PREPARED

- Train GP's and health care workers in Immunization, especially communication skilss in how to respond to vaccine safety concerns to the public and the media
- Rapid response to alleged side effects,
- Government needs to defense immunization programs. Be prepared and able to show benefits of immunization and communicate professionally in case of safety issues
- Include Immunization courses in the curricula of all healthcare workers

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CONCLUSION

HEPB VACCINATION CHALLENGES TO ACHIEVE ELIMINATION OF HEPATITIS B

- Setting a national plan with national goals for hepatitis B control, including vaccination
- With attention for timely vaccination and birth dose
- Vaccination of all persons including high risks
- Building and sustaining support for existing hepatitis B vaccination policies and programmes.

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STILL A LONG WAY TO GO …BUT WE ARE ON THE RIGHT TRACK