Nouveautés VHB – vers l'éradication ?

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JOURNEES MEDICALES 2026
CITE DE LA VOILE, LORIENT
AUDITORIUM

Liens d’intérêt (derniers 12 mois)

- Réunion d’experts: ViiV Healthcare, Gilead, GSK, Abbvie
- Bourse de voyage en congrès: Gilead
- Activités de formation: MSD, ViiV Healthcare, Gilead, Biomérieux, Shionogi
- Financement d’essais cliniques (à l’institution): ViiV Healthcare, MSD, Abbvie, Gilead, GSK

L’hépatite B en 2026, est-ce encore une question d’actualité ?!

- Comment l’épidémiologie éclaire les progrès et les échecs de la lutte contre le VHB
- Rappel sur l’histoire naturelle de l’infection à VHB… pour en comprendre les enjeux de santé publique
- Mise à jour des recommandations de traitement (avant-première AFEF 2026)
- Quid de la co-infection VIH-VHB?
- Quid de la vaccination ?
- Et l’élimination ? Pourra-t-on parler un jour d’éradication ?

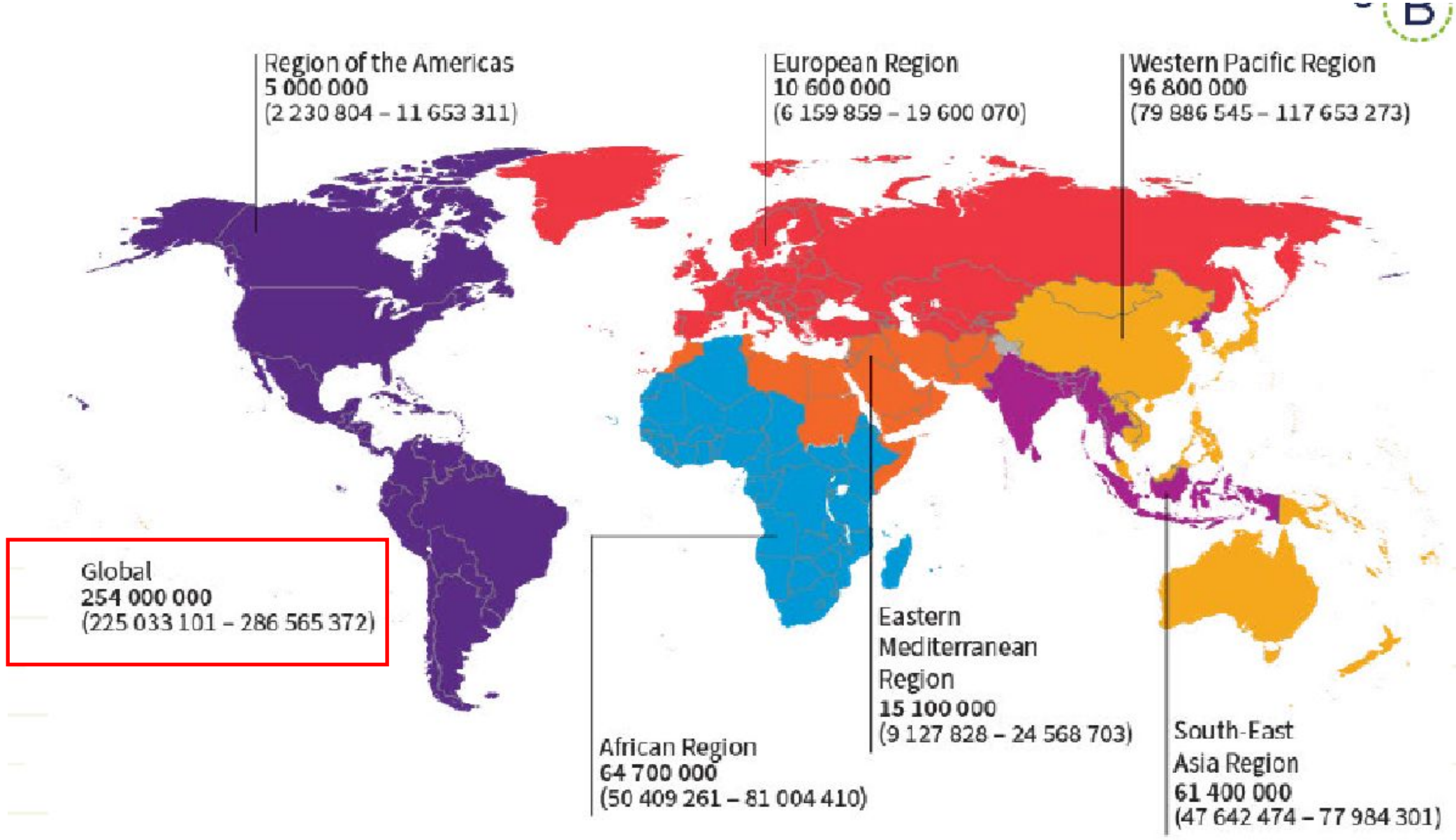
Données actualisées 2024 de prévalence du VHB

WHO region	Prevalence of chronic viral hepatitis B among the general population (%)	Prevalence of chronic viral hepatitis C among the general population (%)	Total hepatitis B infections (all ages)	Total hepatitis C infections (all ages)
African Region	5.8	0.7	64 700 000	7 800 000
Region of the Americas	0.5	0.5	5 000 000	5 300 000
South-East Asia Region	3.0	0.5	61 400 000	9 100 000
European Region	1.2	0.9	10 600 000	8 600 000
Eastern Mediterranean Region	2.1	1.8	15 100 000	11 700 000
Western Pacific Region	5.0	0.4	96 800 000	7 100 000

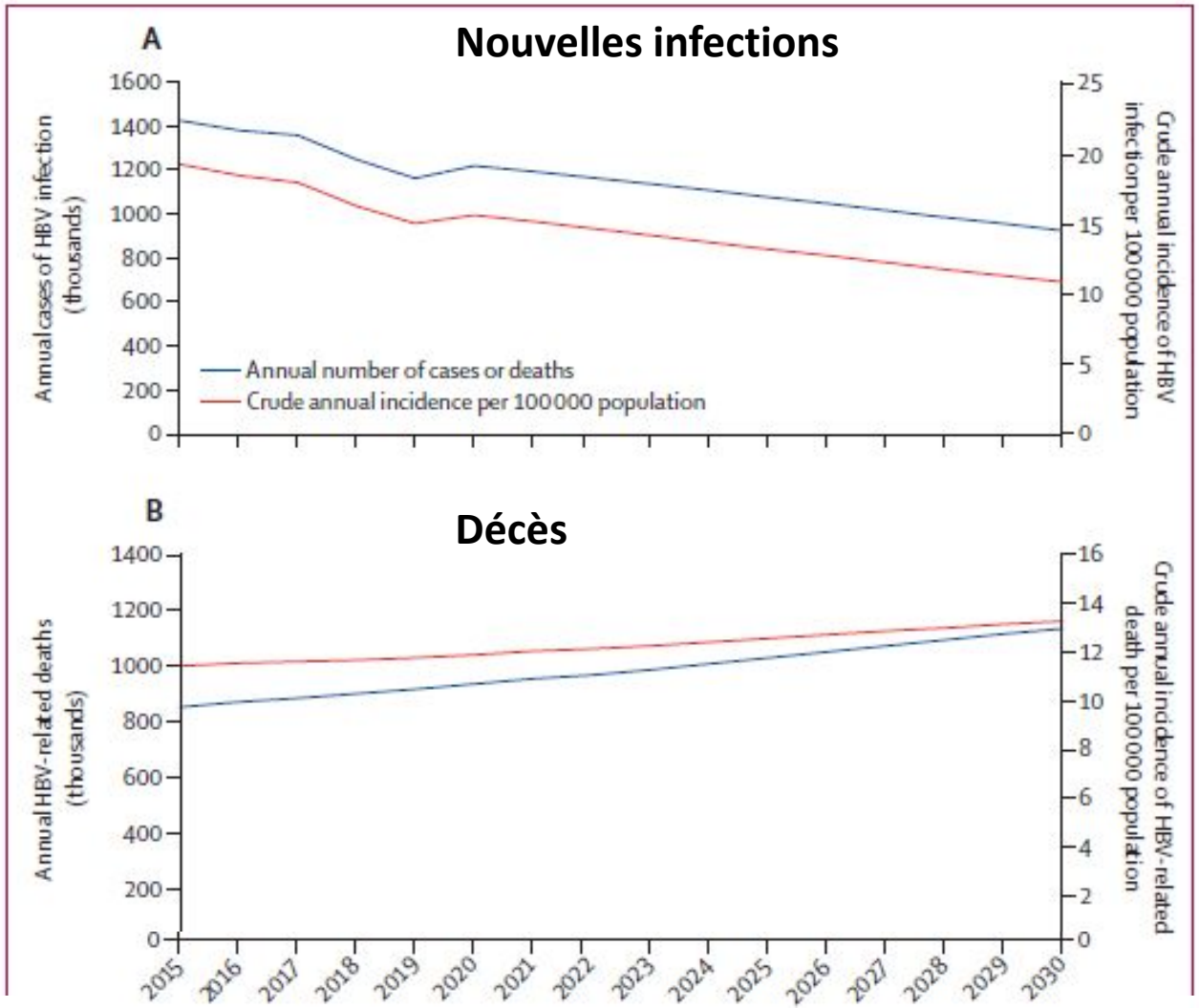
Source: Global Hepatitis Reporting System, WHO.

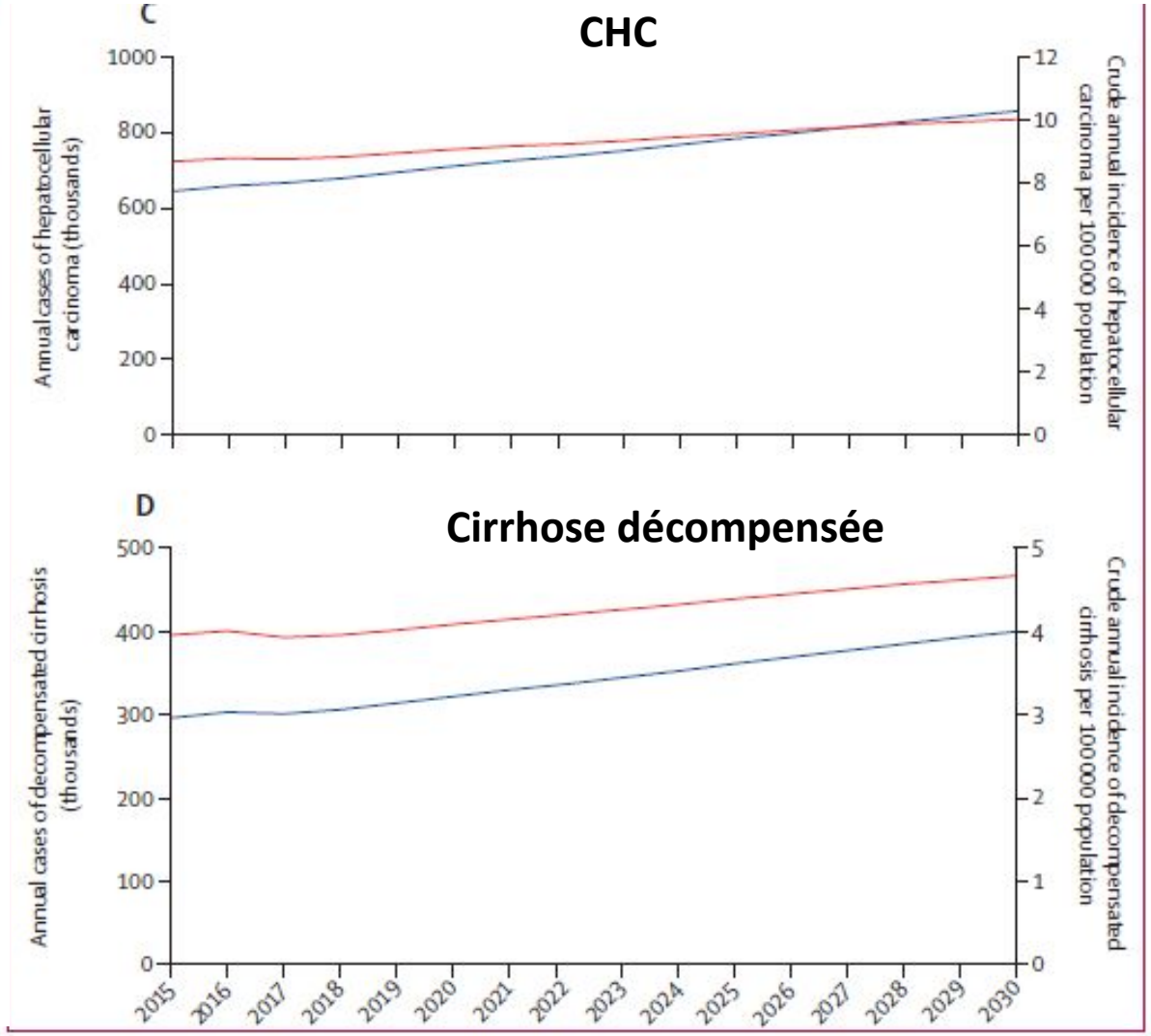
- Diminution globale notable de la prévalence de l'hépatite B chronique dans le monde

https://www.who.int/publications/i/item/9789240091672


Region of the Americas
5 000 000
(2 230 804 – 11 653 311)
European Region
10 600 000
(6 159 859 – 19 600 070)
Western Pacific Region
96 800 000
(79 886 545 – 117 653 273)
Global
254 000 000
(225 033 101 – 286 565 372)
African Region
64 700 000
(50 409 261 – 81 004 410)
Eastern Mediterranean Region
15 100 000
(9 127 828 – 24 568 703)
South-East Asia Region
61 400 000
(47 642 474 – 77 984 301)
African Region
Region of the Americas
Eastern Mediterranean Region
South-East Asia Region
European Region
Western Pacific Region
Not applicable

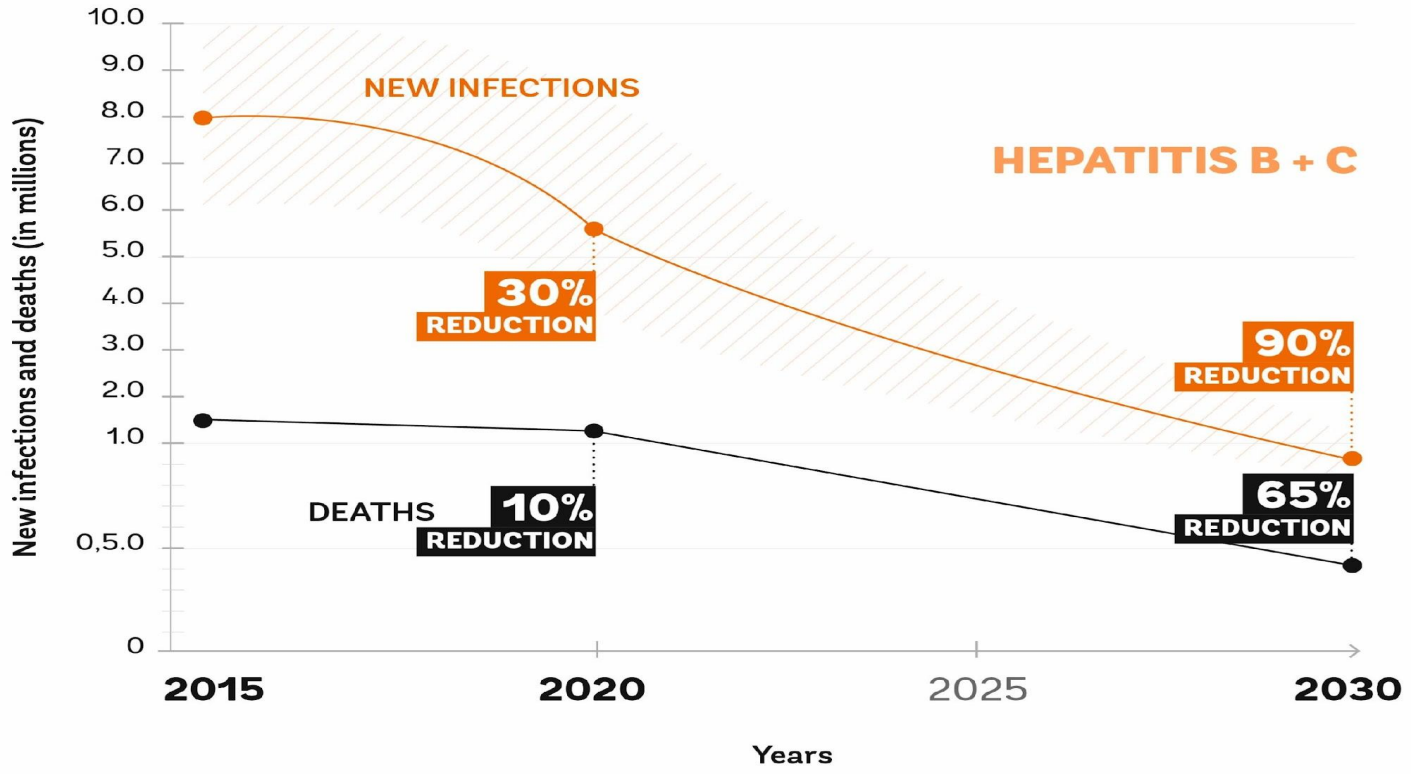
Modélisation de la morbi-mortalité par VHB

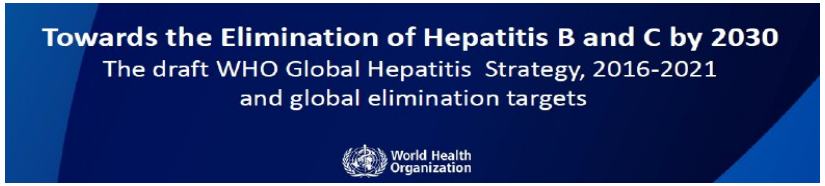




Polaris, Lancet Gastroenterol Hepatol, 2023

SDG (Objectifs OMS de développement durable) pour 2030: élimination des hépatites virales



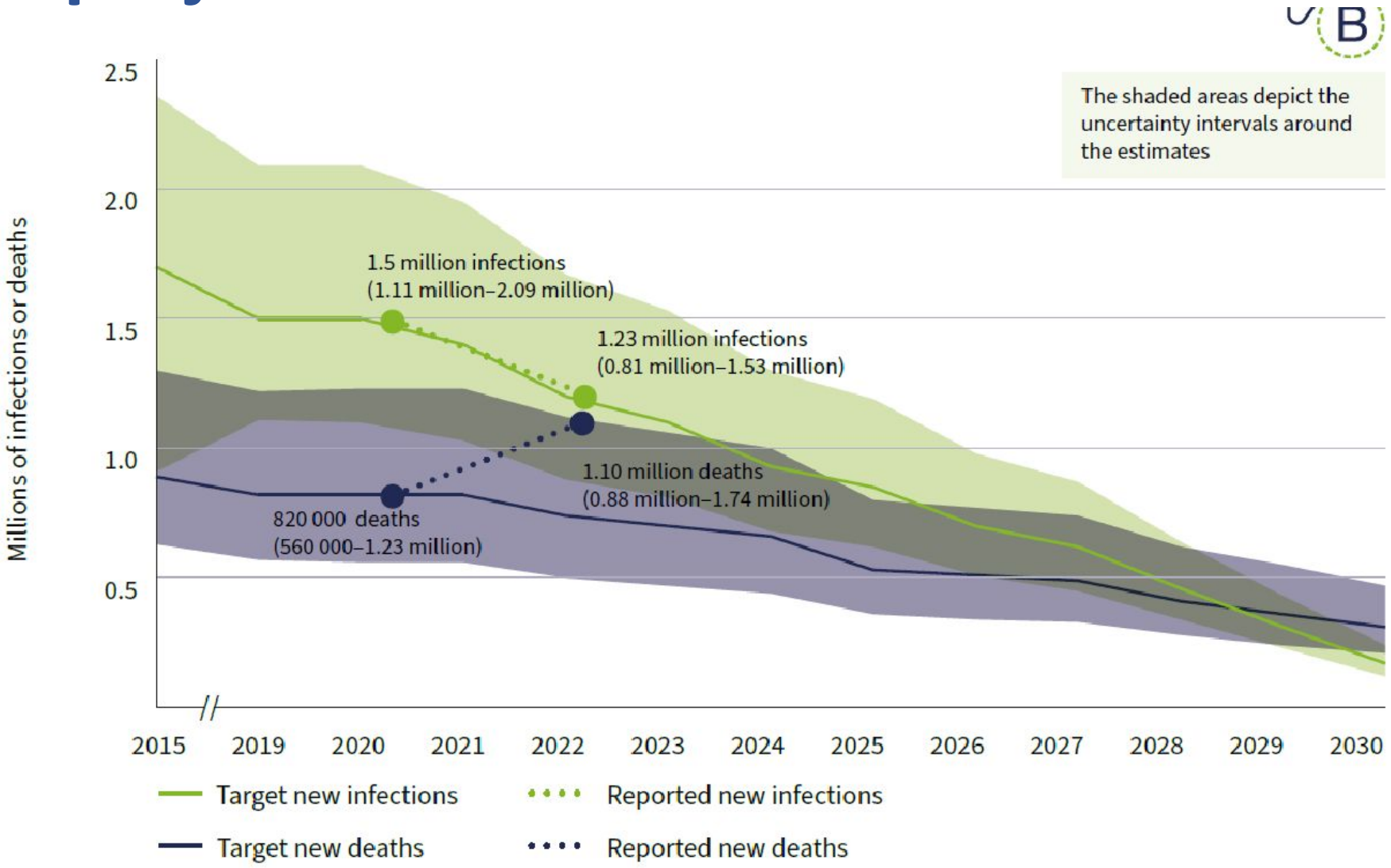


Incidence: □ 6-10 million d'infections (en 2015) à 900,000 infections (d'ici 2030)

Mortalité: □ 1.4 million décès (en 2015) à 500,000 décès (d'ici 2030)

Global Hepatitis Report 2017

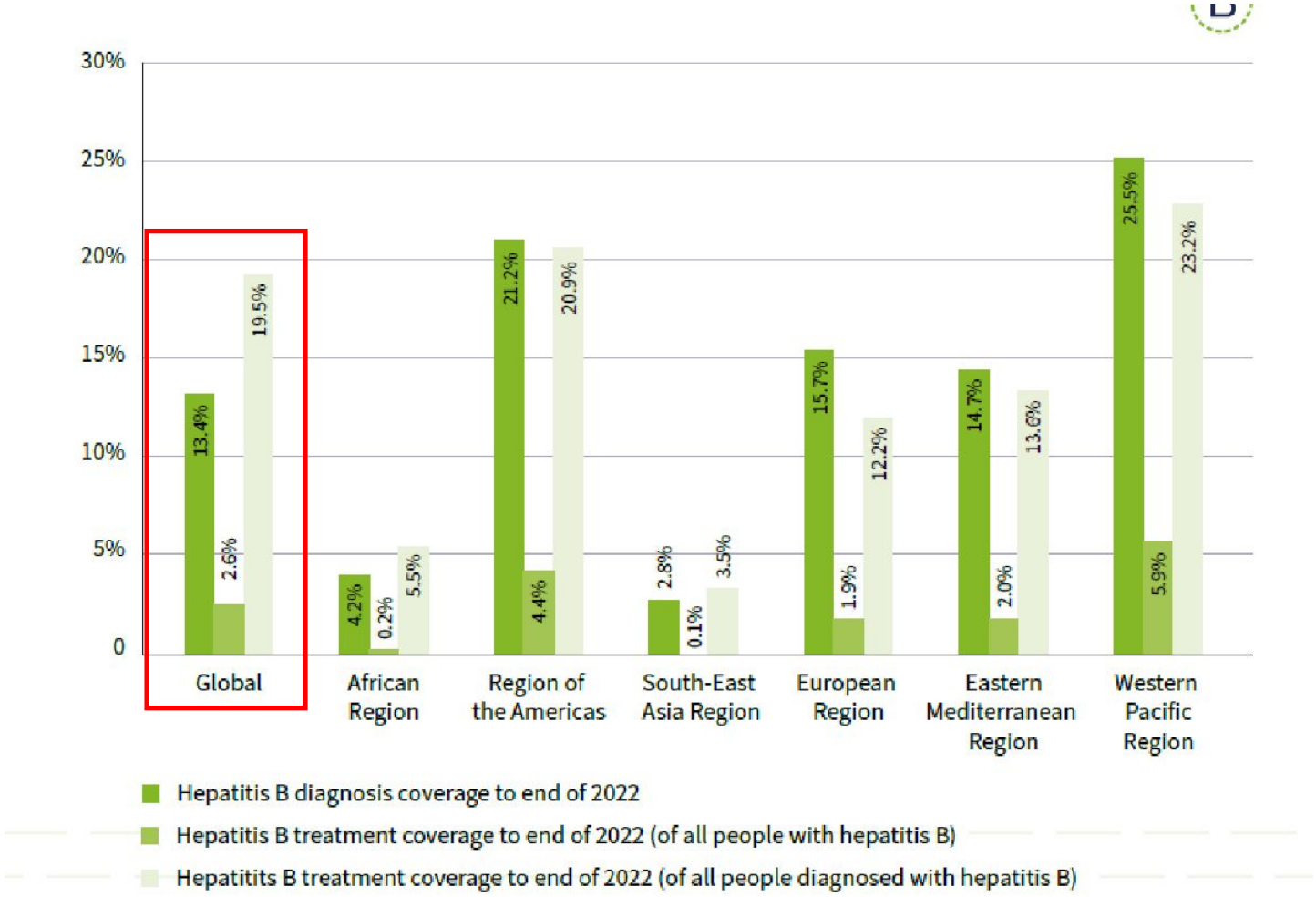
Focus sur la morbi-mortalité entre 2015 et projection 2030



- Certain Succès de la prévention
- Mais échec de l'accès au traitement

https://www.who.int/publications/i/item/9789240091672

Cascade de prise en soins du VHB en 2022



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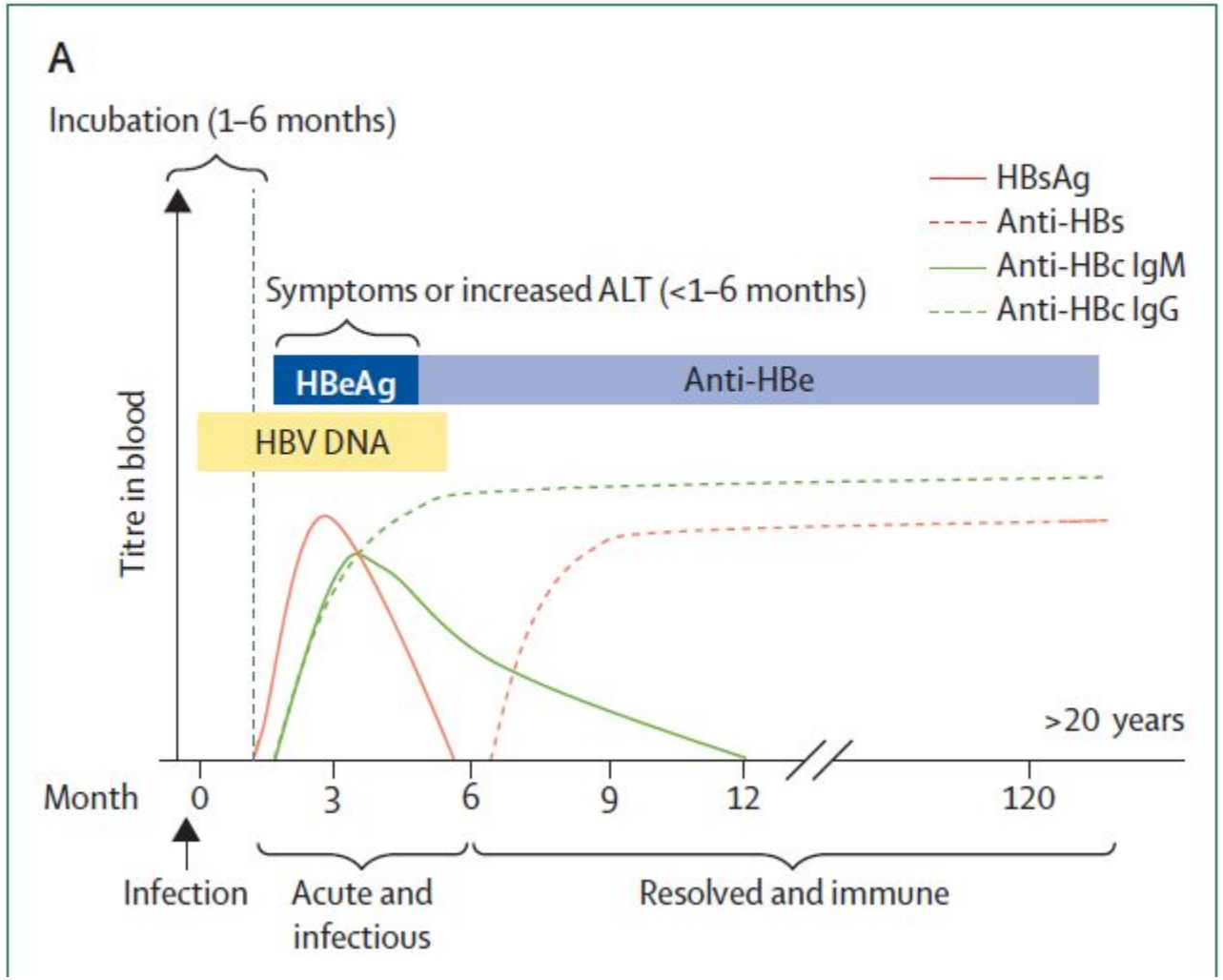
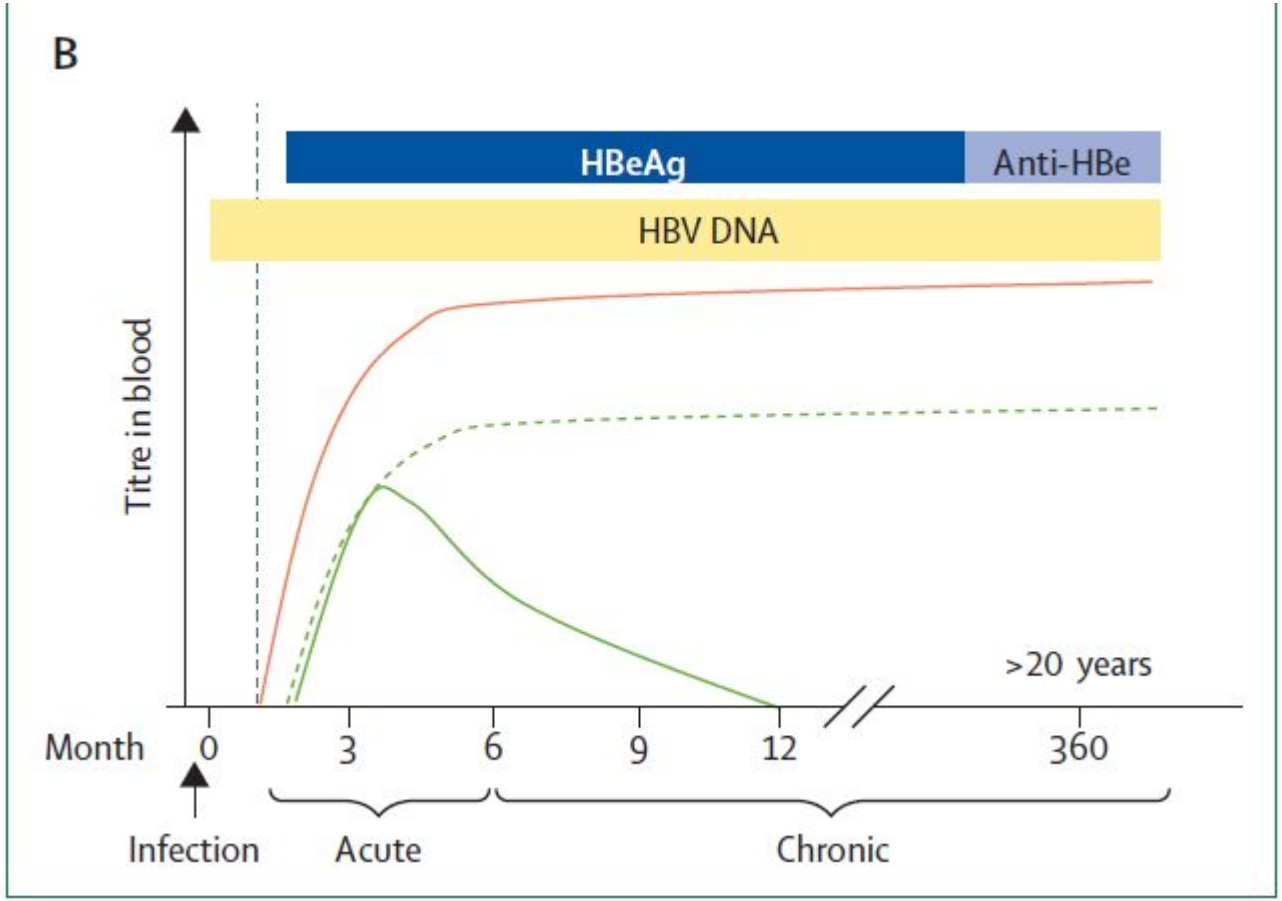
Evolution clinique et biologique: l'hépatite B aigue



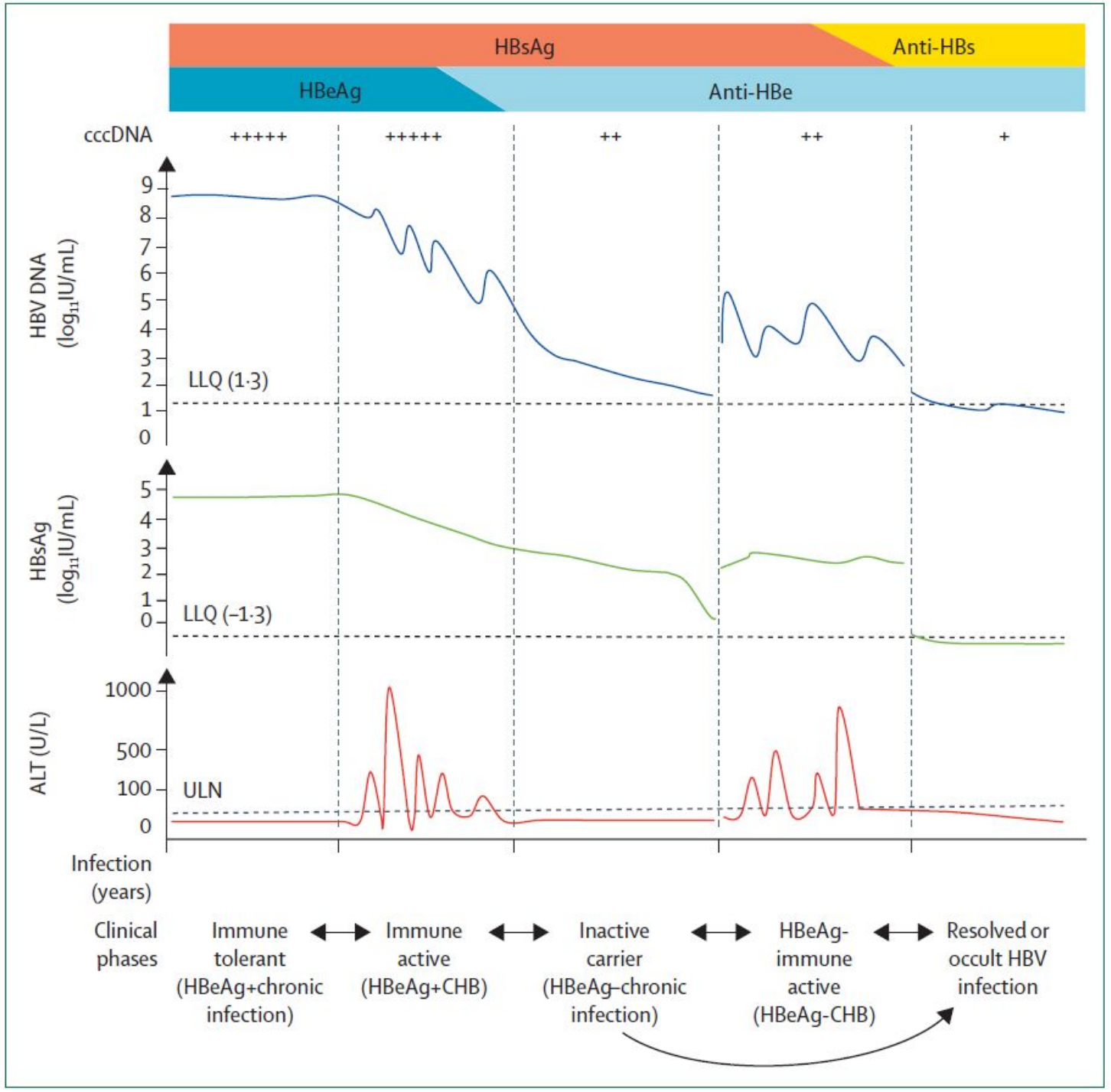
Jeng, Lancet 2023

Evolution clinique et biologique: l'hépatite B chronique



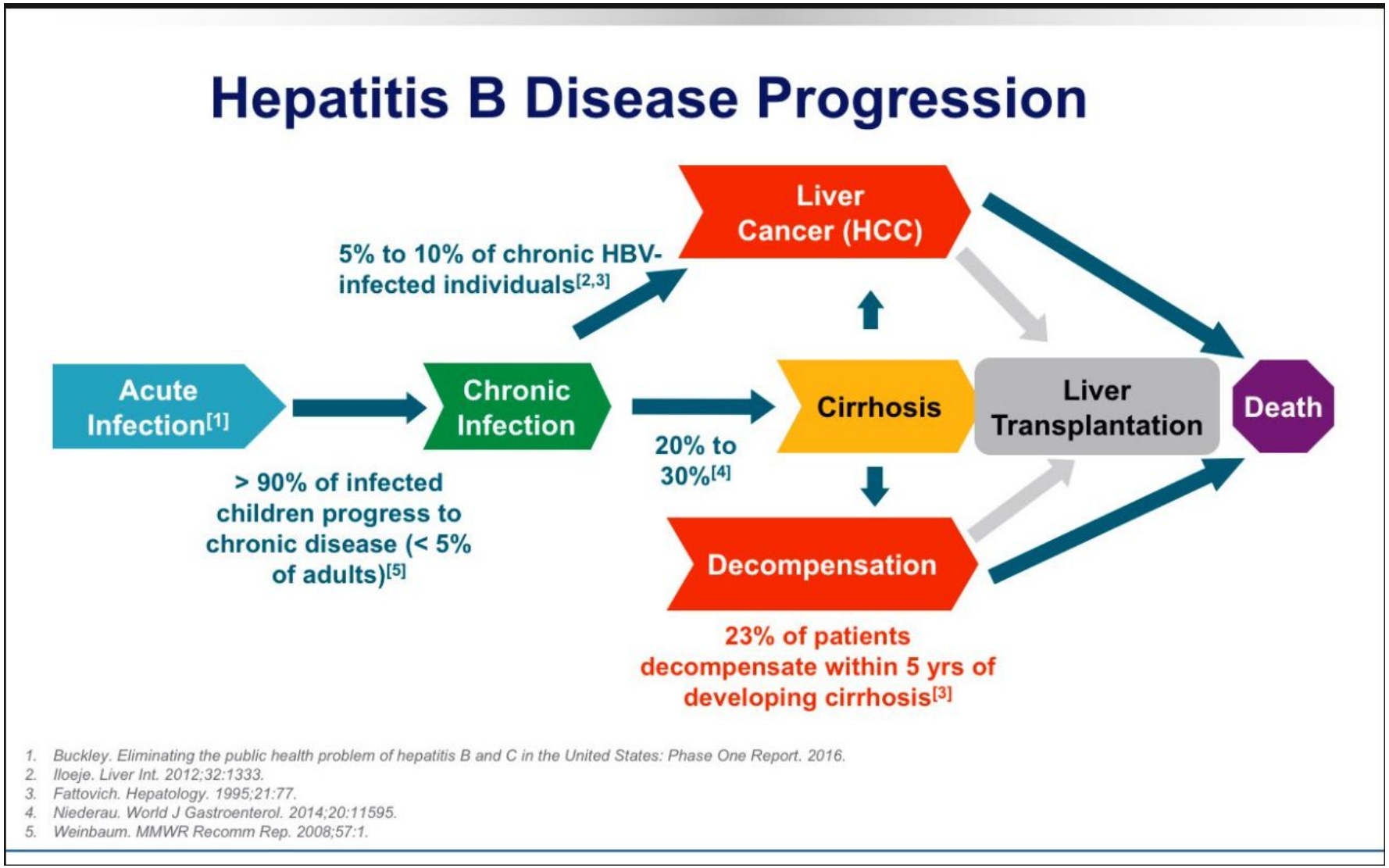
Jeng, Lancet 2023

Histoire naturelle des marqueurs virologiques de l'hépatite B



Jeng, Lancet 2023

Histoire naturelle clinique de l'hépatite B



Nomenclature des états chroniques

	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	High	High/intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	$>10^7$ IU/ml	10^4-10^7 IU/ml	<2,000 IU/ml°°	>2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis

- 5 phases, not necessarily sequencial:
  - Phase 1: HBeAg+ HBV chronic infection (former « immune tolerant »)
  - Phase 2: HBeAg+ chronic hepatitis B
  - Phase 3: HBeAg- HBV chronic infection (former « inactive carrier »)
  - Phase 4: HBeAg- chronic hepatitis B (former « preC mutant hepatitis B)
  - Phase 5: occult hepatitis B

EASL Clinical Preactice Guidelines on the management of HBV, 2017

Et dans le contexte du VIH ?

- Pas d'arrêt du TDF/TAF si AgHBs +
- Risque négligeable de réactivation chez AcHBc+ si simplification de traitement par bithérapie avec 3TC (attention si cirrhose)
- Risque très faible de réactivation chez AcHBc+ si simplification de traitement par association sans XTC ni TDF/TAF, nécessité de suivre les marqueurs sérologiques et ADN-VHB (non si cirrhose)
- Vaccination au cas par cas des patients avec AcAntiHBc + sans Ac antiHBs (pas de preuve de l'efficacité à long terme sur la réponse anticorps)

EACS Guidelines 2025

Limites de la prise en soins actuelle

- Traitement à vie
- Quid de la tolérance après 10, 20, 30 et plus années de NUCs ?
- Observance, qualité de vie ?
- Quid du suivi des personnes non traitées ?
- Quid des règles d'arrêt des NUCs ?
- Risque de réactivation du VHB si immunodépression
- …

Objectif OMS : élimination de l'hépatite B en 2030

Prévention
- Vaccination la plus précoce possible au cours de la vie, adaptée à chaque sujet
- Protection des rapports sexuels
- Matériel à usage unique au cours de la toxicomanie

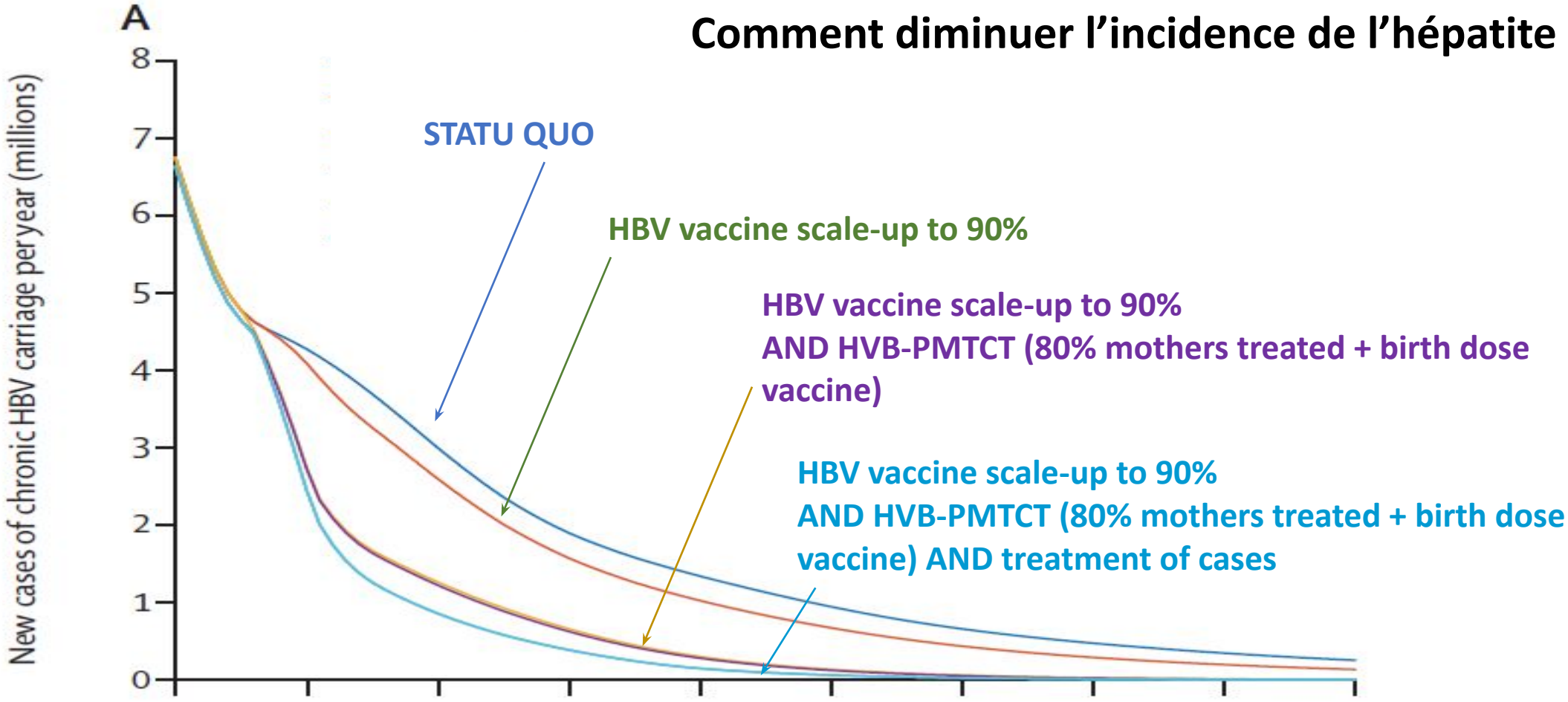
Dépistage
- De tout sujet au moins une fois dans sa vie
- Plus en fonction des facteurs de risque de contamination en l'absence de prévention efficace
- D'autant plus précoce qu'il y a des facteurs de risque géographiques et familiaux

Traitement
- Diminution de la morbi-mortalité
- Prévention de la transmission

Prévention de la survenue de la cirrhose, de ses complications, des manifestations extra-hépatiques

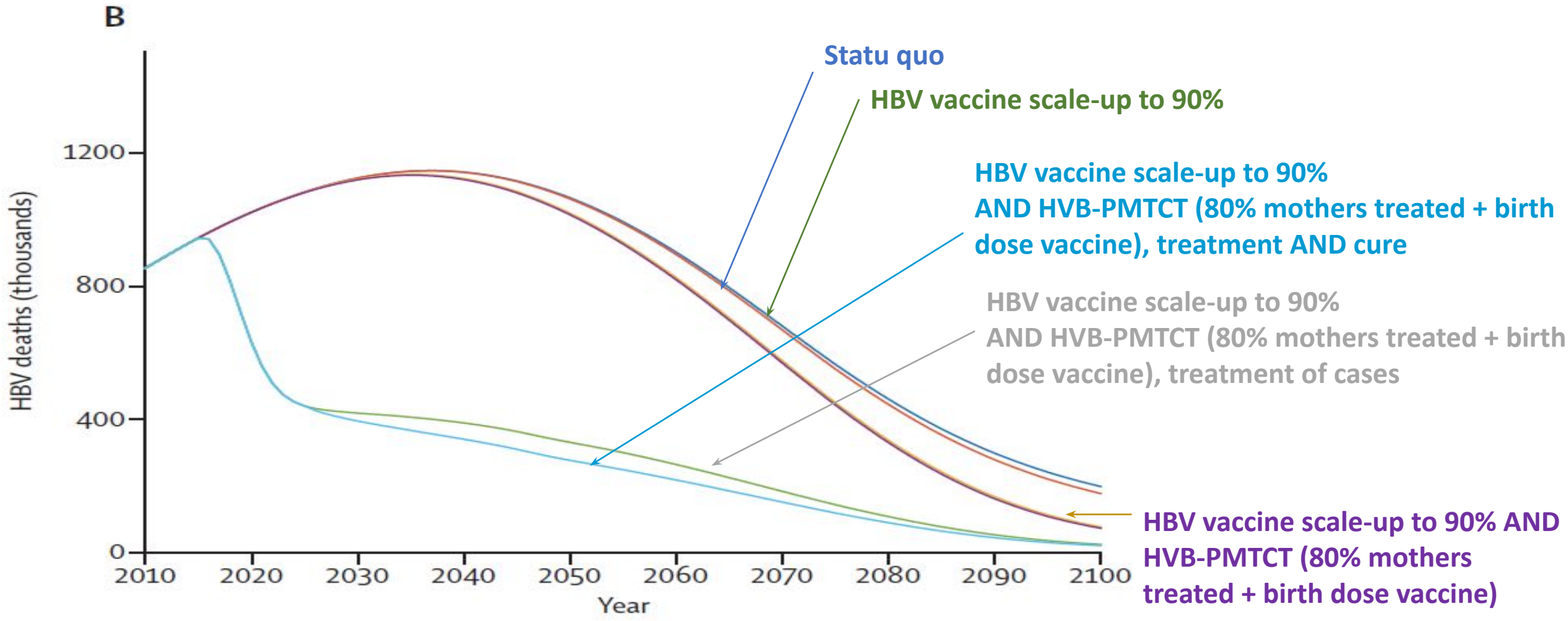
De l'hépatocyte à la santé publique: comment atteindre les objectifs OMS d'ici 2030?

Comment diminuer l'incidence de l'hépatite B?



Nagayam S. Lancet Glob Health 2016

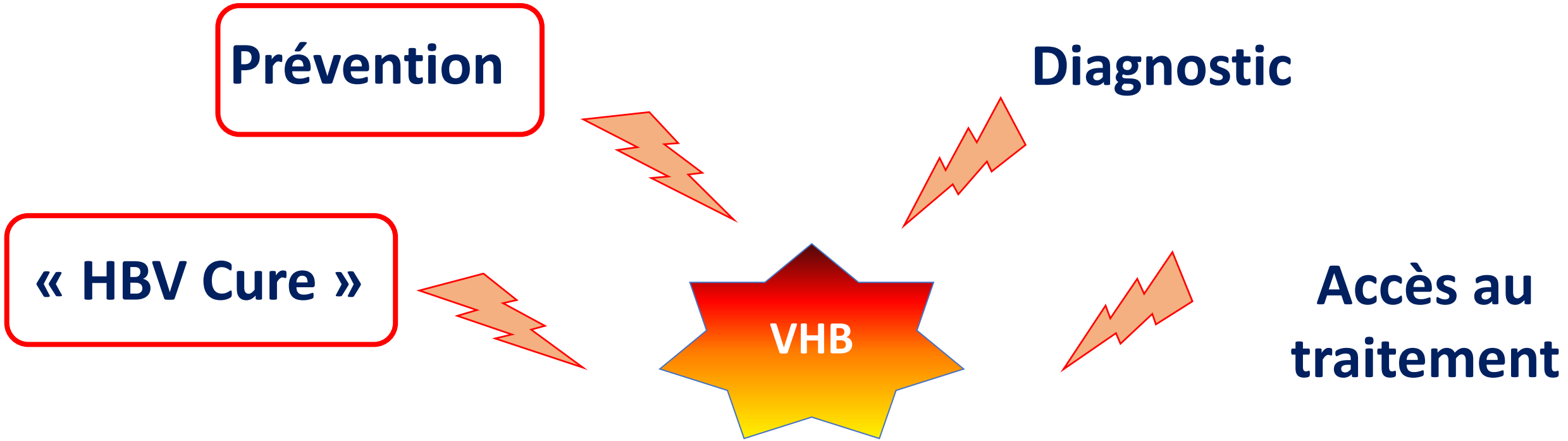
Comment diminuer la mortalité par hépatite B ?



Nagayam S. Lancet Glob Health 2016

Quels outils pour l'élimination de l'hépatite B ?

Sans implémentation d'outils efficaces, entre 2015 et 2030[1]
63 millions nouveaux cas d'hépatite B
17 millions décès liés au VHC



[1]Nagayam, Lancet Glob Health 2016

HEPLISAV-B®
Hepatitis B Vaccine (Recombinant), Adjuvanted

L’espoir d’un meilleur vaccin

- HEPLISAV B is comprised of recombinant hepatitis B surface antigen and the CpG 1018 adjuvant, which is a 22-mer PS-ODN immunostimulatory sequence. HEPLISAV B induces specific antibodies against HBsAg (anti-HBs)

- The biological actions of CpG 1018 are exerted locally at the injection site and draining lymph nodes.

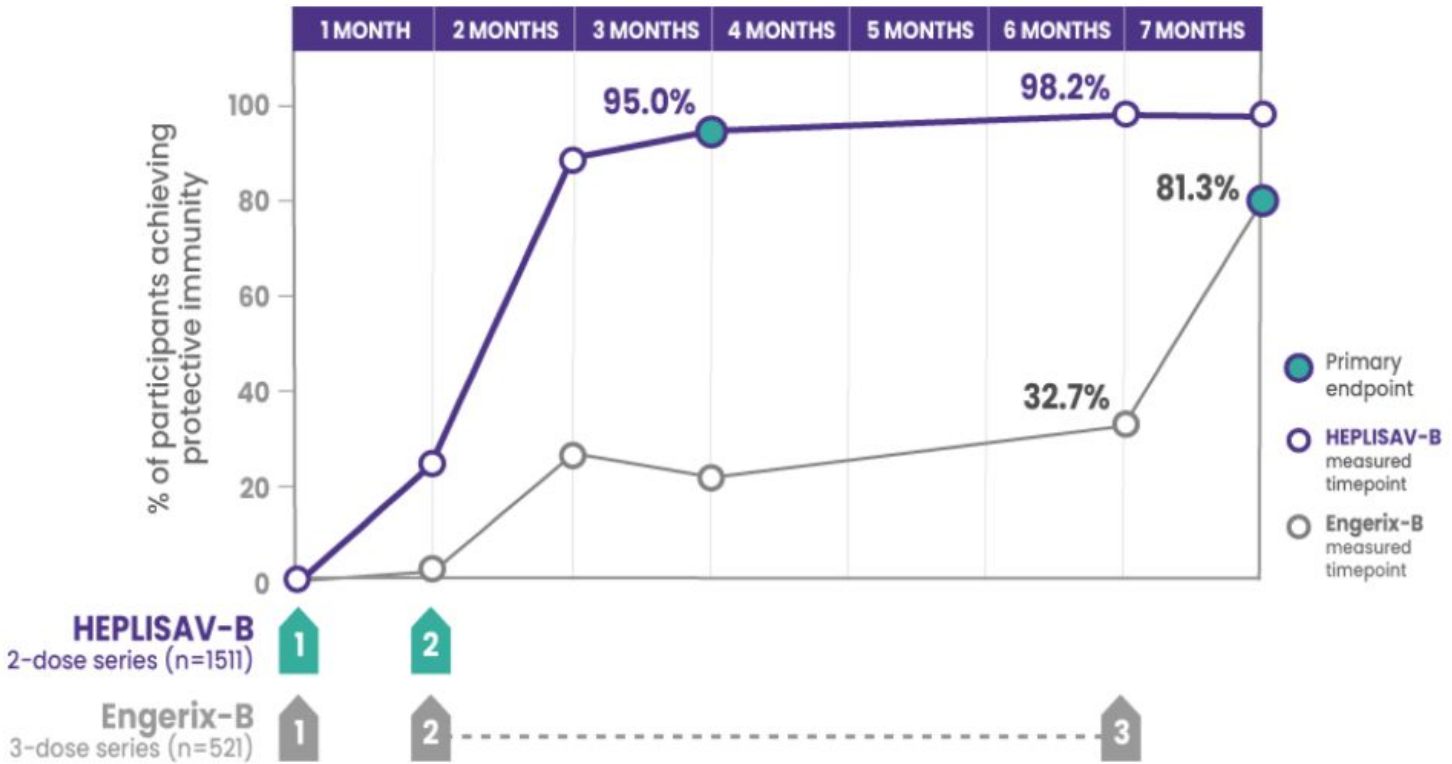
- The adjuvant CpG 1018 component of HEPLISAV B has the following effects:
  - (1) Activates plasmacytoid dendritic cells (pDCs) through the pattern recognition receptor Toll-like receptor 9;
  - (2) converts pDCs into highly efficient antigen-presenting cells that present the processed HBsAg to CD4+ T cells; and,
  - (3) promotes Th1 T-cell differentiation through the production of IFN-alpha and IL-12.

  This activation results in a high and sustained antibody response, likely due to the rapid generation of large numbers of anti-HBs-secreting plasmacytes and HBsAg-specific memory B and T cells.

Study Design

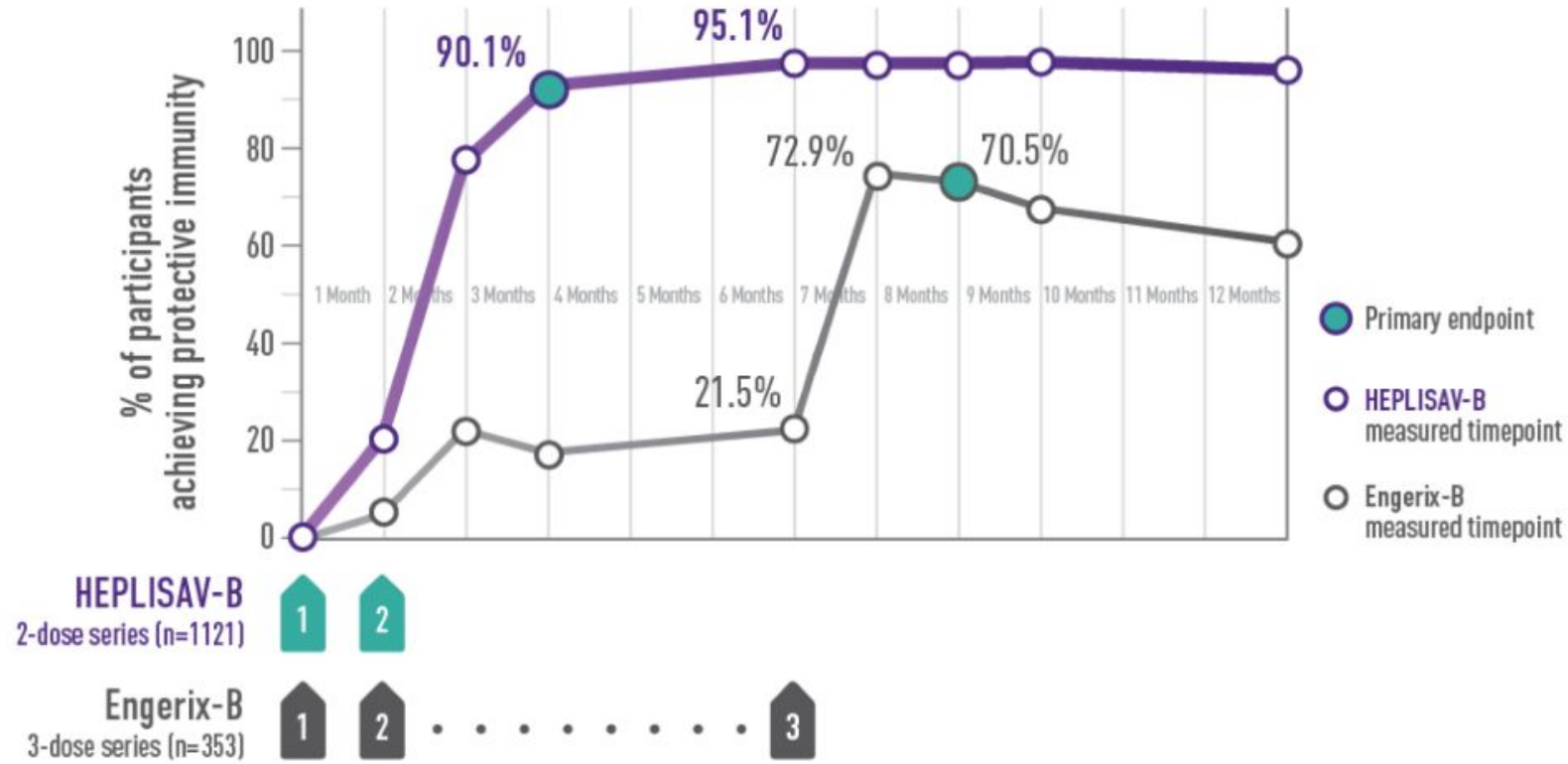
The immunogenicity of HEPLISAV-B was evaluated in comparison with a licensed hepatitis B vaccine (Engerix-B) in 3 randomized active-controlled, observer-blinded, multicenter Phase 3 clinical trials of adults. HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Engerix-B was given at 0, 1, and 6 months. The trials compared the seroprotection rates (% with antibody concentration ≥10 mIU/mL) induced by HEPLISAV-B and Engerix-B.[1]

STUDY 1: Percentage of participants achieving protective immunity†



- Noninferiority was met because the lower bound of the 95% CI of the difference in SPRs was greater than -10%
- 13.7% difference (95% CI, 10.4–17.5) in protective immunity between patient groups at primary endpoint
- The primary analysis compared the rate of protective immunity at week 12 for HEPLISAV-B with that at week 28 for Engerix-B

STUDY 2: Percentage of participants aged **40–70** achieving protective immunity



- 19.6% (95% CI, 14.7–24.8) difference in protective immunity between patient groups at primary endpoint
- The primary analysis compared the rate of protective immunity at week 12 for HEPLISAV-B with that at week 32 for Engerix-B
- Noninferiority was met because the lower bound of the 95% confidence interval of the difference in SPRs was greater than -10%. The SPR following HEPLISAV-B was statistically significantly higher than following Engerix-B (lower bound of the 95% confidence interval of the difference in SPRs was greater than 0%).

	HEPLISAV-B	Engerix-B
PRIMARY ANALYSIS		
DIABETES n=961	90.0%	65.1%
SECONDARY ANALYSIS		
TOTAL TRIAL POPULATION n=6665	95.4%	81.3%
MALE n=3353	94.5%	78.8%
AGED 60 TO 70 n=1745	91.6%	72.6%
OBESITY n=3241	94.7%	75.4%
SMOKERS n=2082	95.9%	78.6%

Trial 3 study design: A clinical trial in adults aged 18 to 70 years who received HEPLISAV-B (n=4376) or Engerix-B (n=2289).

- The primary analysis compared the seroprotection rate at week 28 for HEPLISAV-B (n=640) with that at week 28 for Engerix-B (n=321) in subjects with type 2 diabetes mellitus. Noninferiority of the seroprotection rate induced by HEPLISAV-B compared to Engerix-B was demonstrated.
- A secondary analysis compared the seroprotection rate at week 24 for HEPLISAV-B with that at week 28 for Engerix-B in the total study population. Noninferiority of the seroprotection rate induced by HEPLISAV-B compared to Engerix-B was demonstrated.
- Other secondary analyses compared the seroprotection rate at week 24 for HEPLISAV-B with that at week 28 for Engerix-B, in subgroups defined by age, sex, body mass index (BMI), and smoking status among adults aged 18 to 70 years. For each subgroup noninferiority of the seroprotection rate induced by HEPLISAV-B compared to Engerix-B was demonstrated.

BEe-HIVe: Study Design

- Multicenter, prospective, open-label, randomized phase III trial

Group A stratified by diabetes and sex at birth

Adults with HIV-1 infection; aged 18-70 yr; currently on ART; CD4+ cell count ≥100 cells/mm^3; HIV-1 RNA <1000 copies/mL; HBV antibody nonresponsive, indeterminate, or <10 mIU/mL and prior HBV vaccination within >168 days (Group A); no prior HBV vaccination (Group B) (N = 640)

Prior Nonresponse (Group A)

Vaccine Naive (Group B)

- **2-Dose HepB-CpG*** at Wk 0 and 4 (n = 187)
- **3-Dose HepB-CpG*** at Wk 0, 4, and 24 (n = 187)
- **3-Dose HepB-alum†** at Wk 0, 4, and 24 (n = 187)
- **3-Dose HepB-CpG*** at Wk 0, 4, and 24 (n = 73)

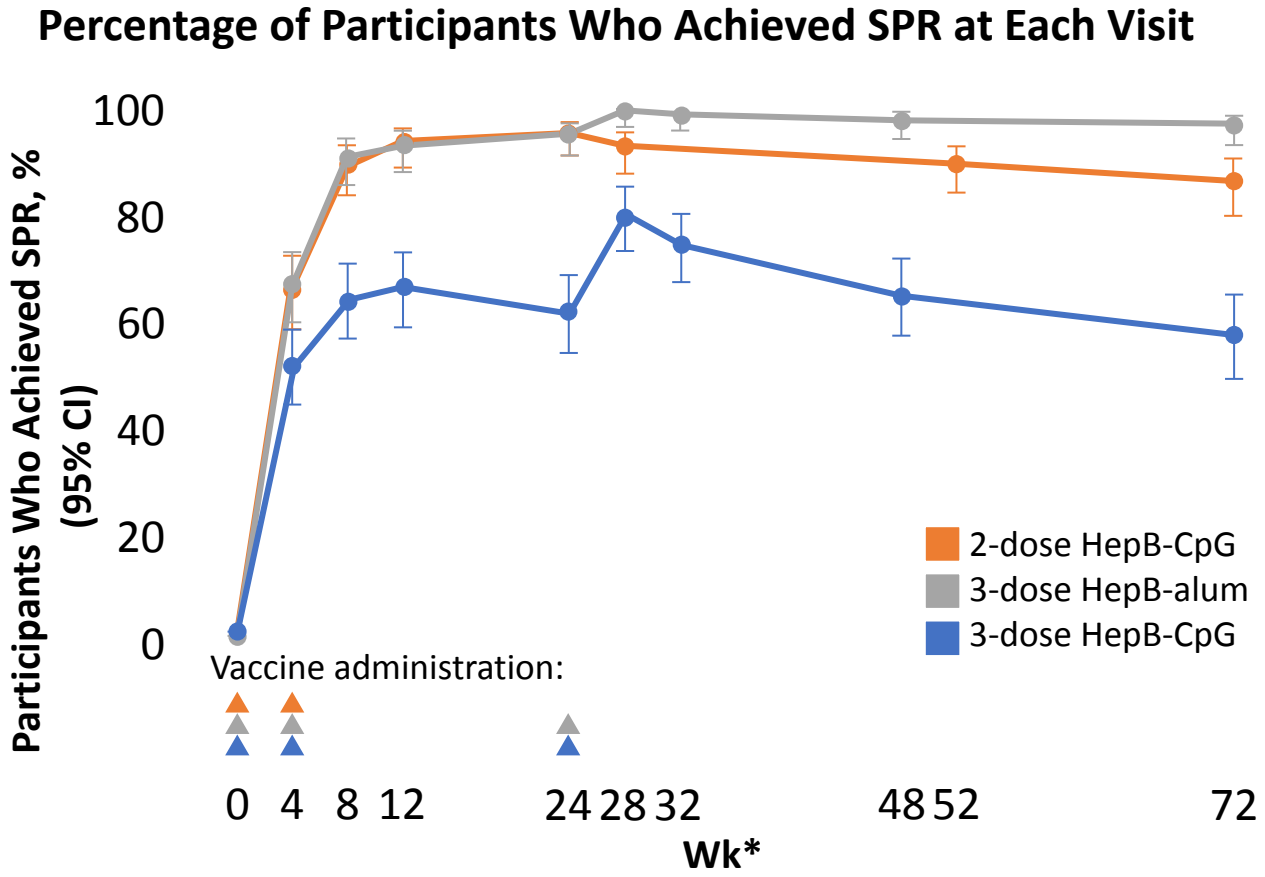
Study end at Wk 72

*HBsAg 20 mcg + CpG 1018 3000 mcg in 0.5 mL, IM.
†HBsAg 20 mcg in 1.0 mL, IM.

- **Durability study endpoints:** estimation of difference in the end-of-study SPR proportions (Group A); estimation of the end-of-study SPR proportion (Group B)

NCT04193189. Marks. CROI 2025. Abstr 112.

BEe-HIVe: SPR (HBsAb ≥10 mIU/mL) in Prior Nonresponse Group Over Time

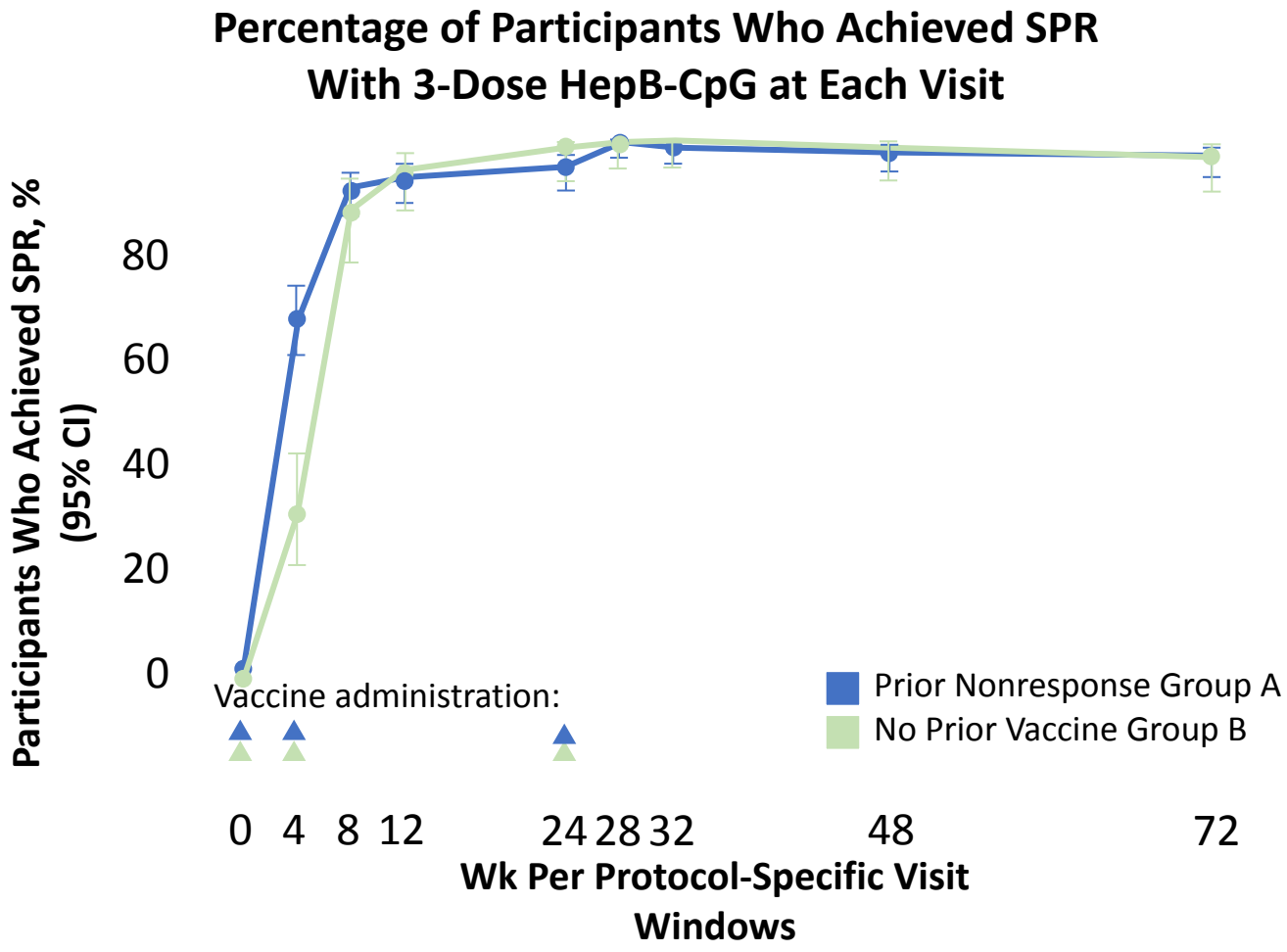


- Participants who achieved SPR at Wk 72:
  - 97.2% with 3-dose **HepB-CpG**
  - 86.1% with 2-dose **HepB-CpG**
  - 57.5% with 3-dose **HepB-alum**
- Participants who achieved SPR at any point but had HBsAb <10 mIU/mL at Wk 72:
  - 2.1% with 3-dose **HepB-CpG**
  - 10.7% with 2-dose **HepB-CpG**
  - 22.0% with 3-dose **HepB-alum**

*Time (wk) per protocol-specific visit windows; visiting schedules were different between 2-dose vs 3-dose study arms.

Marks. CROI 2025. Abstr 112. Reproduced with permission.

BEe-HIVe: SPR in Prior Nonresponse Group vs Vaccine Naive Group



- Durability in no prior vaccine Group B:
  - **SPR at Wk 28:** 100% (94.7% CI: 95%-100%)
  - **SPR at Wk 72:** 97.3% (95% CI: 90.7%-99.3%)
- HBsAb ≥10 mIU/mL with 3-dose **HepB-CpG** at Wk 72:
  - **No prior vaccine Group B:** 97.3%
  - **Prior nonresponse Group A:** 97.2%

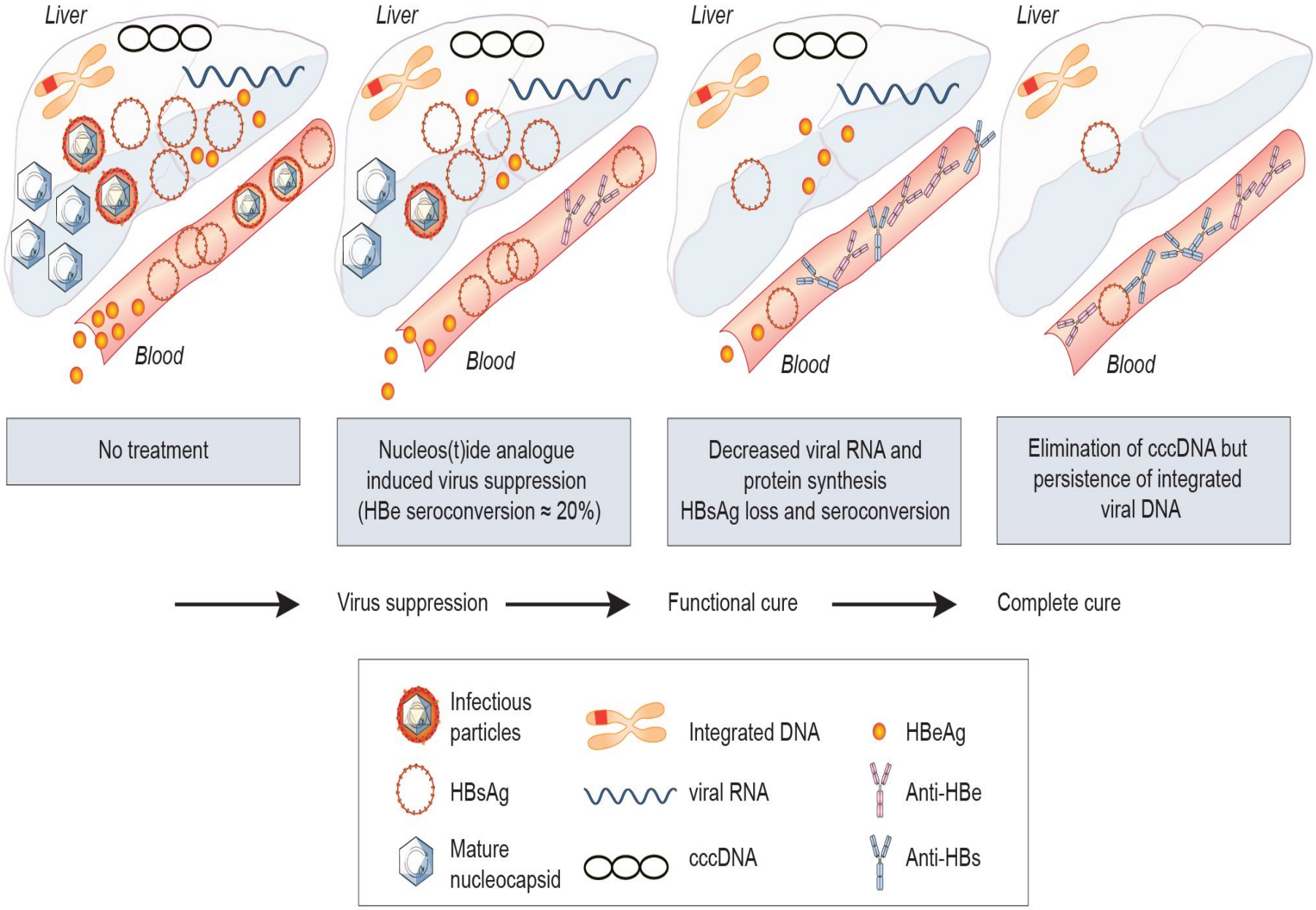
Marks. CROI 2025. Abstr 112. Reproduced with permission.

Ou en est-on de la recherche sur l'éradication du VHB ? Le concept de HBV Cure

- **Cure dite « fonctionnelle »**
  - Situation où le traitement antiviral peut être arrêté sans danger pour le patient
  - Perte de l'AgHBs avec séroconversion HBs (présence d'Ac atiHBs)
  - ***Inactivation du cccDNA*** ou contrôle de sa réplication par les défenses immunitaires de l'hôte

- **Cure dite « complète »**
  - Perte de l'AgHBs, séroconversion HBs et ***éradication du cccDNA***

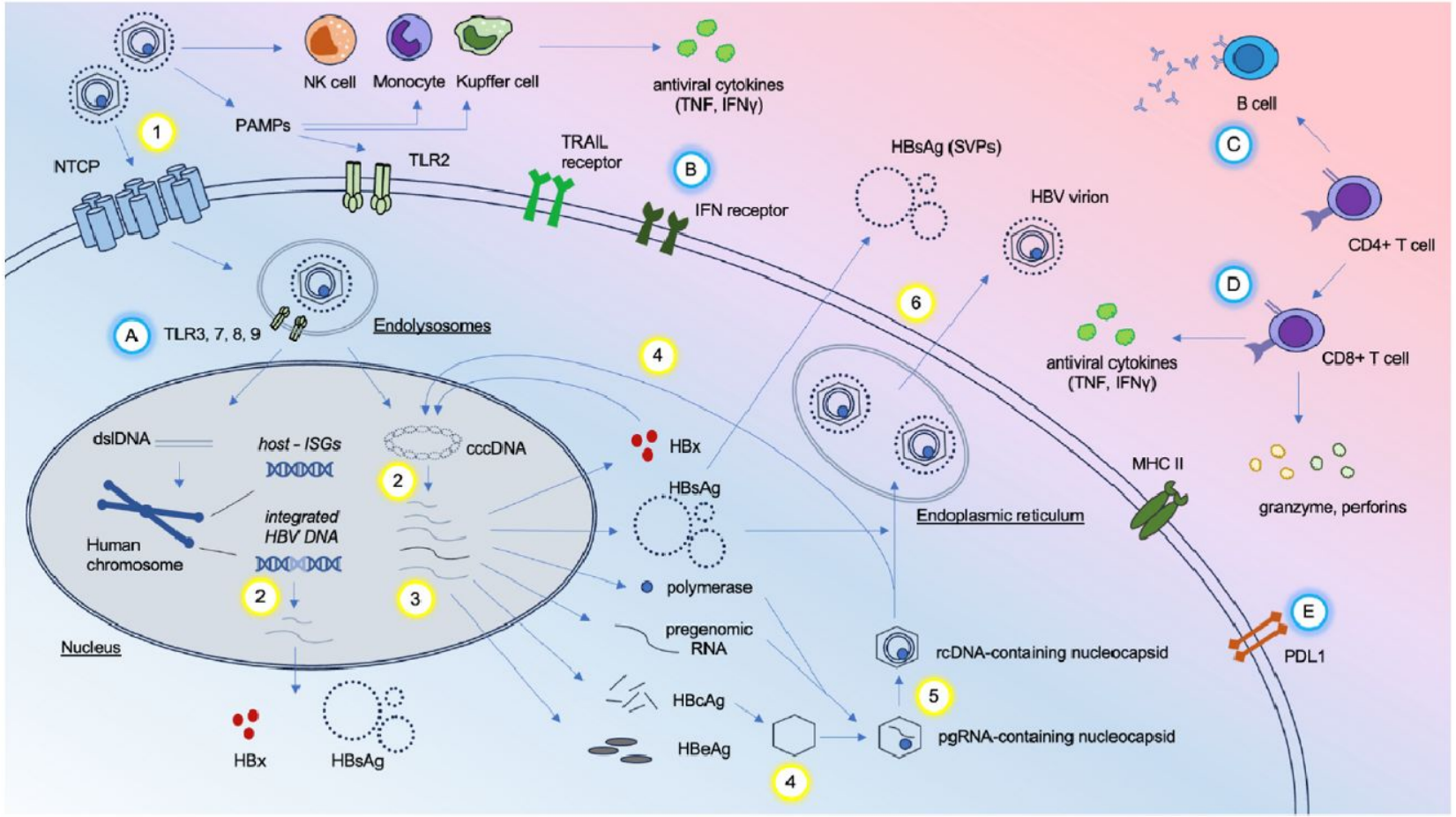
Zeisel, Lucifora et al, Gut 2015; Revill et al, Nature Reviews Gastroenterol Hepatol 2016



Durantel & Zoulim, J Hepatol 2016; Zeisel, Lucifora et al, Gut 2015; Revill et al, Nature Reviews Gastroenterol Hepatol 2016

Multiples sites thérapeutiques hôte / virus

Les cibles antivirales et molécules en phase 2 au minimum

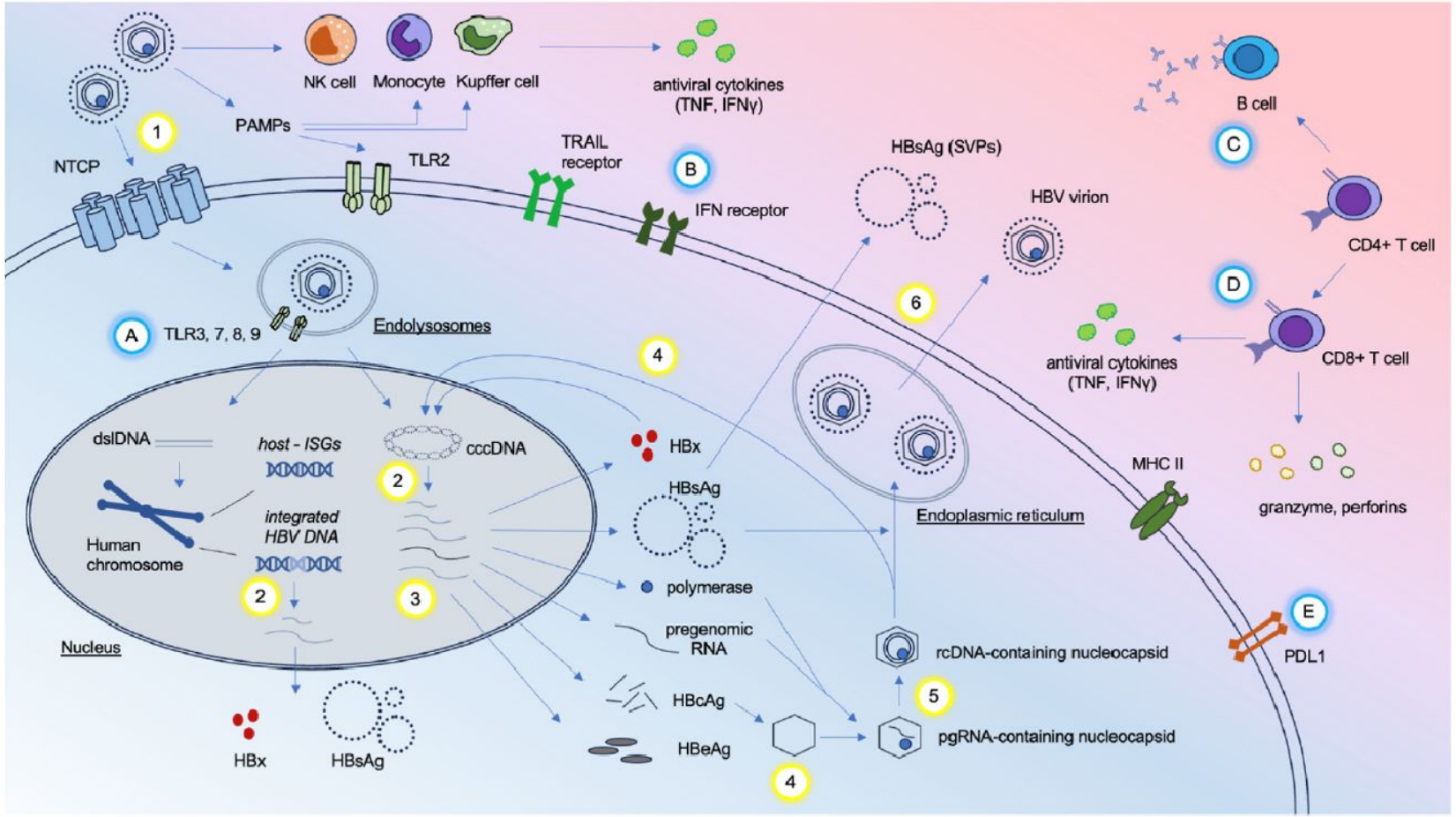


1) Blocage entrée: bulevirtide
2) Rend silencieux le cccDNA (gene editing comme CRISPR CAS9) ou modification épigénétique
3) Vise les transcripts viraux pour rendre silencieux le cccDNA (bépirovirsen)
4) Bloque l'assemblage de la capside (ALG184)
5) Bloque l'ADN polymerase (TDF-ETV)
6) Induit une dégradation lisosomale et protéosomale des particules virales (REP2139)

Mak, Antivir Res 2026

Multiples sites thérapeutiques hôte / virus

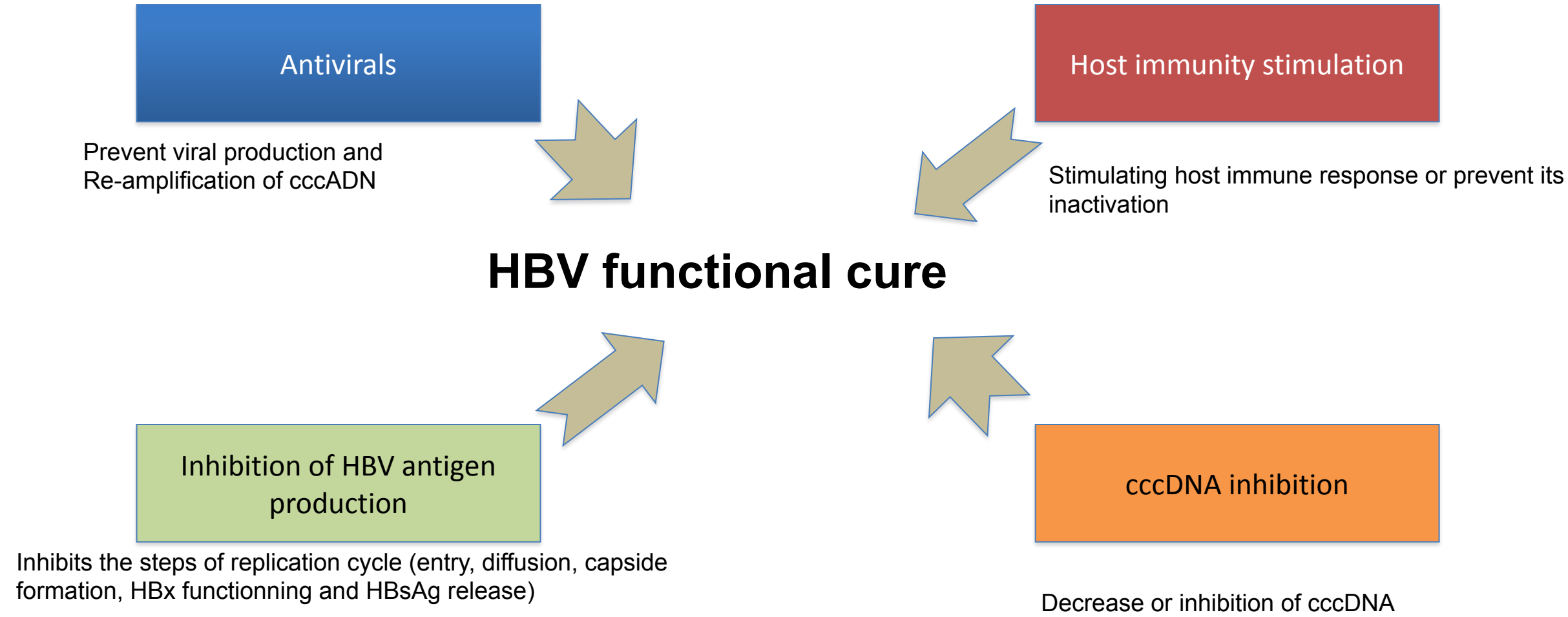
Les cibles immuno-modulatrices et molécules en phase 2 au minimum



A) Classe des TLR médiateurs de la production de cytokines antivirales (vesatolimod)
B) Récepteur IFN régulant l'expression des ISG a effet antiviral (PegIFN)
C) Anticorps monoclonaux facilitant la phagocytose (tobevibart, telovirug, lenvervimab)
D) Vaccins boostant la fonctionnalité des LyCD8+ spécifiques (VRON 0200, TherVacB)
E) Anti PD1 médiant l'interaction PD-PDL1 conduisant à l'exhaustion cellulaire médiée par les LyT (nivolumab, envafolimab)

Mak, Antivir Res 2026

Stratégies prometteuses de guérison (au moins fonctionnelle) ?



Paccoud O. et al. Rev Med Int 2019

Merci !