N. meningitidis Serogroup B Vaccines:

Present status & perspectives

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Public Health Significance

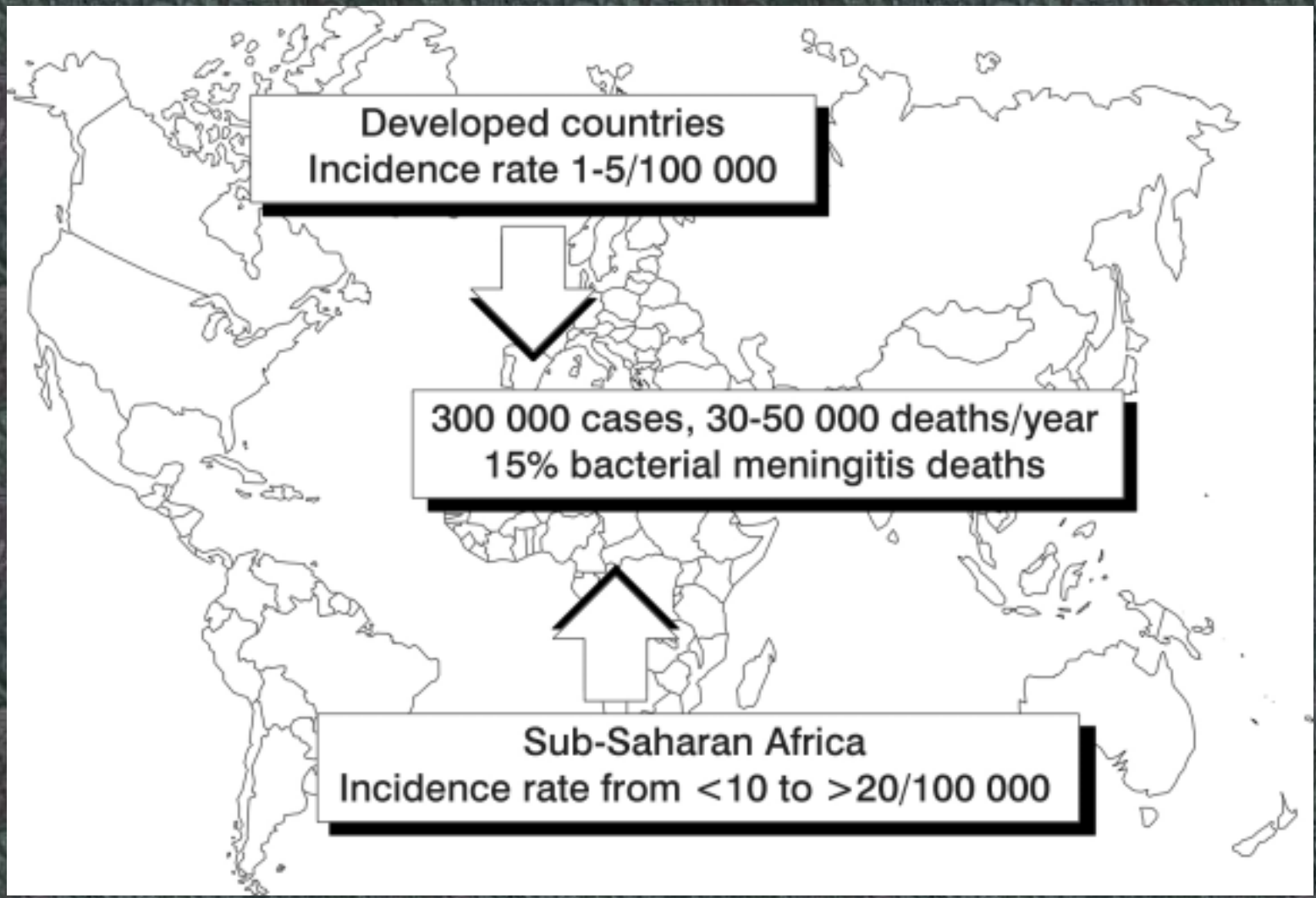
Bacterial meningitis remains a serious threat to the global health

Estimated	~	180 000 people die from bacterial meningitis (Hib, Nm, SN) (Murray CJL, 1996)
Only meningococcal meningitis		300-350000 cases/year Over 30-50000 deaths/year
Men A	~	Epidemics from $10/10^5$ – $400\text{-}800/10^5$
Men B&C		More prevalent as endemic & hyperendemic periods but also causing epidemics (WHO)
Only in USA		3000 cases & ~300 death/year 46% ~50% Men B

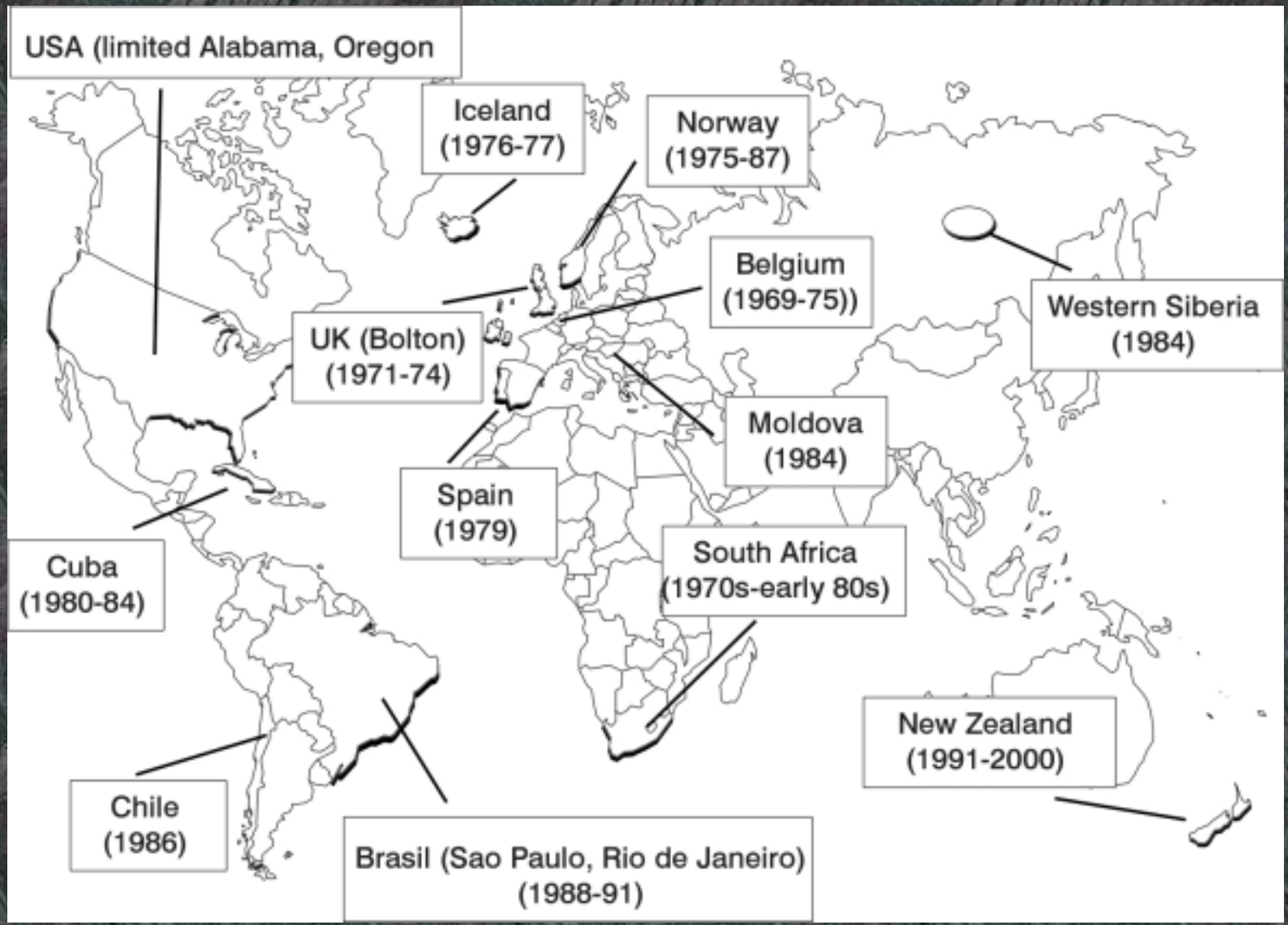
Meningococcal Meningitis

- Acute infective illness,rapid onset.
- Most common;acute purulent meningitis.
- Less common;meningococcal septicaemia,
- Fever,fulminant haemorragic rash,shock
- Crude mortality rate (DCs)7-10%.
- N.Meningitidis;the only bacterium capable of generating epidemic meningitis.

Meningococcal disease: estimates on global disease burden Endemic & hyperendemic conditions



Major outbreaks of meningococcal meningitis B (1979-2000)



Main epidemics of meningococcal meningitis serogroup B (1970-2000)

Country Area	Year/Starting	Attack Rate
Faroe Island	1980-81	95.0
Norway	1975-1987	23.9
Iceland	1976	37.7
Spain	1979	17.9
The Americas		
Brazil, Sao Paulo	1990	14.2
Chile, Iquique	1986	31.2
Cuba	1980-84	14.4
Western Pacific		
New Zealand	1991-2000 (cont.)	17

Meningococcal disease:
Case fatality rates in developed countries

Study	Patient Group	No. Patients	CFR (%)
Wolf & Birbara (1968)	Military recruits	112	7.1
Andersen (1978)	All ages	124	7.4
Oloen et al. (1979)	All ages	69	7.2
Hansman (1983)	All ages	85	8
De Wal et al. (1984)	Children	309	6.1
Fallon et al. (1984)	All ages	1912	7.5
Haltensen et al. (1987)	All ages	211	8.5
Voss et al. (1989)	Children	122	7
Wong et al (1989)	Children	100	10

Average: 7.6%

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Meningococcal disease: trends and challenges

Evolution of case-fatality rates over time

Havens et al (1989)
Ambrosch & Staneck (1980)

30 years study CFR constant at 10.3%
20 years study CFR constant at 8.6%

Evolution of saepticemia rates

Riordan et al (1995)

17 year study showed proportion of saepticemia cases increasing from 7% 1977-85 to 36% 1990-93

Evolution of antimicrobial resistance

Oppenheim et al (1977)
Botha (1988)
Fontanals et al (1989)

Increasing resistant strains to penicillin
Insertion of β-lactamase into genome?

Vaccines versus other strategies

- Mortality rate has not changed significantly during the past 30 years, despite modern antimicrobial treatment & intensive care in special units.
- Inadecuacy of other strategies and the positive experience in some L.A. countries with outbreaks vaccinating with the cuban vaccine.
- Feasebility of MenB vaccination!

Vaccines against meningococcal B disease

I. Capsular approach:	Conjugated modified B polysaccharide
II. Non-Capsular Approach:	Subcapsular Antigens (Proteins & LPS)

I. Capsular approaches

- **Polysacharide B**, T-cell independ Ag:

  fail to induce immunological memory & IgG isotope change ➤ **poorly immunogenic**

- Structural homology with neural cell adhesion molecule (NCAM) prevalent embrionic & newborn brain: considerable concern for **potential induction of autoimmunity**

Ia. Non covalent complex OMP(s) + BPoly

(Zollinger et al 1979, Lifely et al, 1991)

Ib. Covalent conjugated vaccine candidates.

Chemically modified B poly (Jenning et al, 1986) Fusco et al 1997)

N-propionyl B poly conjugated with OMP class 3 (Fusco et al, 1997)

HMW B poly conjugated to TT or CRM_{197} (Bartolomé et a., 1995)

E. Coli K92 Poly conjugated to TT (Davi et al, 1991)

Seven formulations of conjugated PolyB vaccines

Vaccine formulation	Source	Poly B dose	Adjuvant
B poly + OMP (non covalent)	WRAIR	30 µg	Alum
B poly ~ CRM_{197} (conjug)	Biocine – Sclavo	5 µg	None
N prop. E. Coli K1 ~ rPorB	NAVA	5 µg	Alum
		5 µg	S. Tyr
Bpoly ~ OMP	CBER-FDA	5 µg	None
		5 µg	MPL
E. Coli K92 ~ TT	CBER-FDA	5 µg	None

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Immunogenicity trial

- Juvenile rhesus monkeys 1 year old.
- Three doses I.M. (0,6,14weeks).
- GBPS-mHSA___ELISA.
- Variation in Ab level among individual monkeys.
- GBPS conjugated failed to induce SBA.
- 1994…..

Capsular Approach: Present situation

- Poly B conjugated vaccines have elicited Ab immune response in animal models (different potency according to formulation adjuvant, dose, etc.)but not SBA.
- Main concern of all these candidate vaccines is their safety (No obvious adverse reactions were observed even in controlled trials in monkeys)
- NAVA in 1997 reported SBA in african green monkeys using their conjugated vaccine
- Based upon existing investigations is not possible to assure if this vaccine candidates will be free from immunopathological side effects
- No human trials have been yet performed(Conjugated).

MenB Vaccines:

II. Non-Capsular Approach

IIa: Existing vaccines

- **WRAIR (OMP + CP + $Al(OH)_3$) F III Trial (Chile & Stop**
- **Norwegian (OMV + $AL(OH)_3$) F III + now cont. Clinical develop.**
- **Cuban (OMV + CP + $Al(OH)_3$) F III + massive campaign in Cuba and Latinamerica**

IIb: Modified OMP(s), specific OMP(s): under preclinical & inicial clinical development

- **Class I OMP(s): RIVM (mono, hexavalent)**
- **Iron-regulated prot: Tbp(s): Aventis**
- **Class 5 OMP(s): OPA & OPC**
- **Lip (H.8 Ag)**
- **Hia (adhesin, NspA)**

MenB Vaccines:
II. Non-Capsular Approach

IIc: LPS detoxified:

- **Oligo + protein**
- **LPS + liposomes**
- **LPS + OMP(s)**

IId: Nasal vaccine candidates (OMV(s): Cuba, Norway, USA, UK

II. Non-Capsular Approach

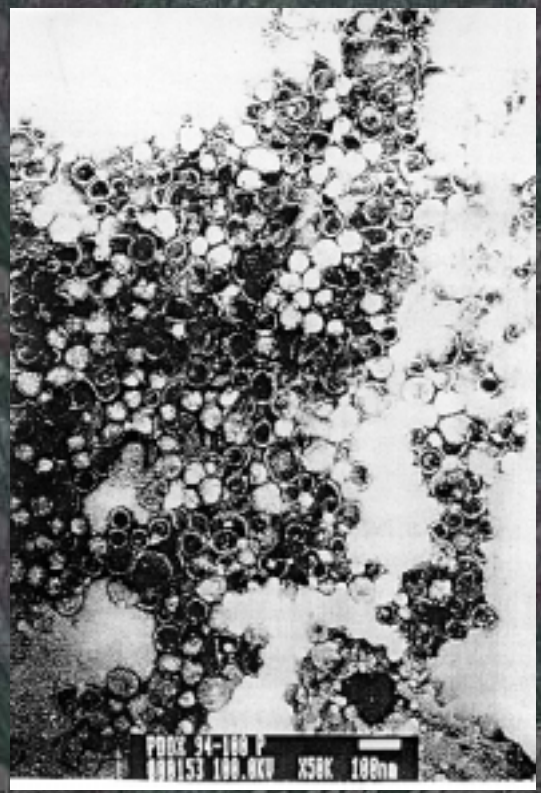
Hard data supporting vaccine efficacy & safety of existing vaccines (Fase III main trials)

Vaccine	Place/Year	T/Study	Dosing	Efficacy
I. Finlay (Cuba)	Cuba/87-89	Double blind placebo-vaccine controlled trial	2x50 µg	83% (10-14 y)
Wrair (USA)	Chile/87-89	Double blind placebo vaccine T	2x100 µg	-39% (1-4 y) 70% (5-21 y)
NIPH (Norway)	Norway/88-91	Double blind	2x25 µg	57% (14-16 y)

MenB: Existing Vaccines

Vaccine	Present Status
Wrair (USA)	F III tested in Iquique, Chile, 51% global efficacy -39% (1-4 y), 70% (5-21 y) Development stopped, no further use.
NIPH (Norway)	F III tested in Norway 57% Efficacy. Further developed. Now a new clinical development FI – II – III under way
I. Finlay (Cuba)	F III tested in Cuba, 83% Efficacy. Massively used in Cuba, epidemic controlled. Field (FIII, IV) tested in Brazil, Colombia, etc. Massively used in Latinoamerican countries 45 000 000 doses applied. Licended in 17 countries Industrial scale up completed under GMP(s) Included in the Vaccination Schedule in Cuba

I. Finlay Vaccine: First Proteoliposome-based Vaccine



Purified outer-membrane vesicles of serogroup B meningococcus	50 µg
Purified capsular polysaccharide of serogroup C meningococcus	50 µg
Thiomersal	0.05 mg
Phosphate salts	0.05 mg
Sodium chloride	4.25 mg
Water for injection, sq	0.5 ml
Aluminum hydroxide gel	

I. Finlay Vaccine: Some clinical experiences

Place/Year	Age Group	T/Study	Results
7 Provinces/Cuba* (1987-89)	10 – 14y	Prospective, doble blind controlled	83%
Ciego de Avila* (1989-90)	3m – 5y	Retrospective, open cohort study	81%
14 Provinces/Cuba*	3m – 5y	Case control retrospective	81%
Rio de Janeiro/Brazil** (1990-92)	6m – 9y	Case control retrospective	< 2y – 53% 2 -3y – 77% 3 - 9y – 80%
Sao Pablo/Brazil** (1990-91)	3m – 6y	Case control ambispective	< 2y – 37% 2 -4y – 47% >4y – 74%
Antioquia/Colombia* (1990-92)	3m – 5y	Prospective cohort study controlled	98%

* Homologous strains

** High % of heterologous strains

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I. Finlay Vaccine: Clinical impact in Cuba

Clinical attack rate before vaccination	$14.4/10^5$
Clinical attack rate after vaccination	$0.01/10^5$
Attack rates in more affected age group	0 – 6 y
before vaccination	$48 – 120/10^5$
after vaccination	$0.01 – 0.05/10^5$
Reduction impact	93 %

Epidemic controlled vaccine included in Immunization Programm

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OMV – Based vaccines

Limitations & Advantages

PROS	CONS
• The first vaccine to complete pharmaceutical & clinical development up to industrial production • The only licenced & commercially available (VA-MENGOC-BC®) • Safe • Very efficacious controlling outbreaks & epidemics • Massive clinical experience (45000000 doses) • 83% efficacy with 2 doses will be higher with 3 doses schedule under trial	• Lower protection rates in infants below 2 years of age against heterologous strains (but even in this condition offer significative protection) • Need for brooder spectrum in young infants

Other vaccines under development

From the rest of vaccine candidates the more advance one to continue clinical development are:

* RIVM hexavalent (P1)^{6} recombinant (Hexamen)
* RIVM monovalent (P1) recombinant (P1.7h.4)

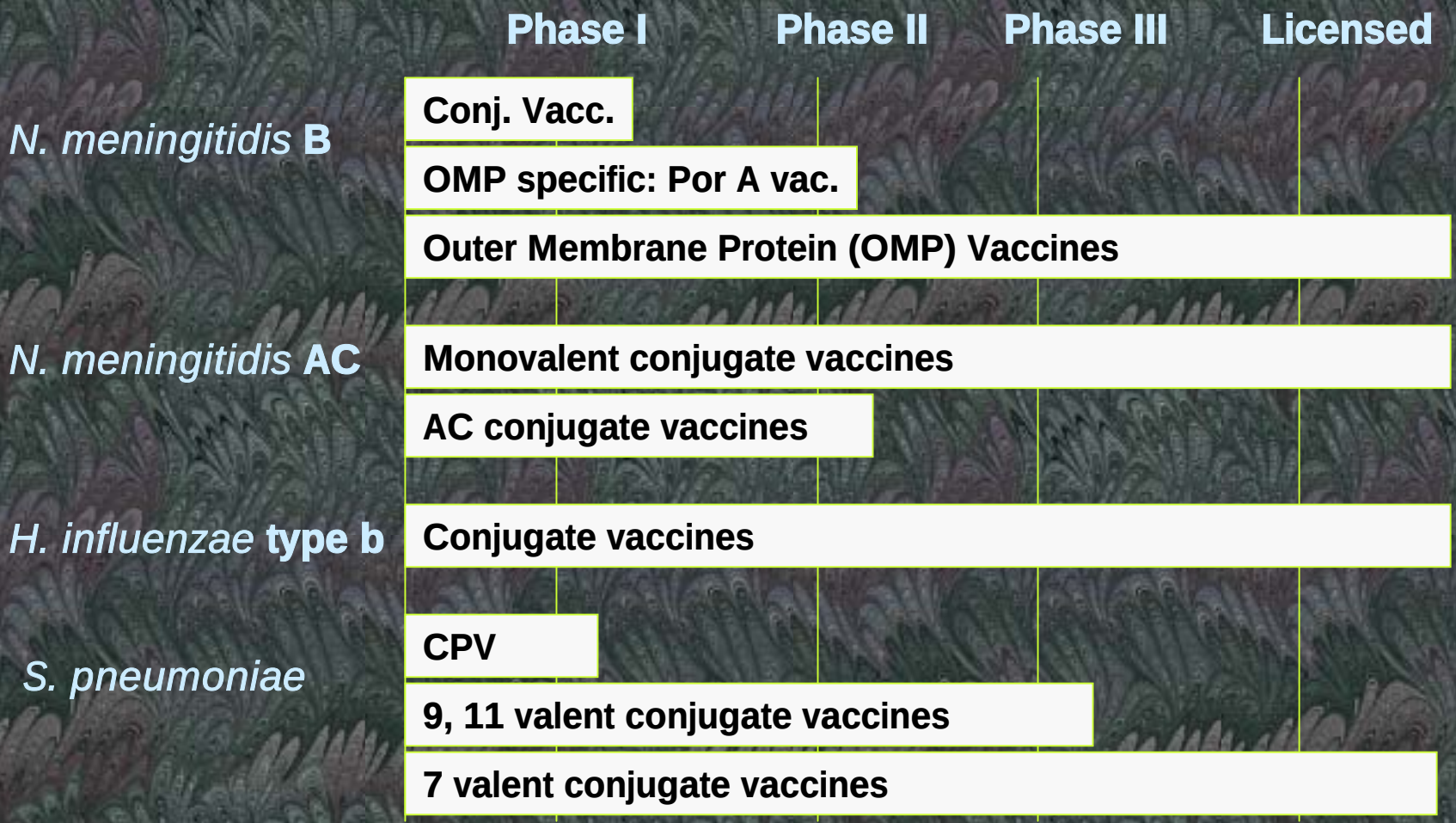
- 4 vaccinations with Hexamen / 90% SBAx4) monovalent is immunogenic in infants and boostes the Hexamen response
- Some aspects have to be developed as well as the completion of clinical evaluation

Antimeningococcal vaccines: future prospects

- **MenB – OMV vaccine generation:** Based on vesicular – proteoliposome technology (FINLAY'S patent) with broader spectrum against circulating sero-subtypes. (I. Finlay – GSK).
- **New MenB – Vaccine generation:** Based on "in sílico" Ag discovery in the menB genome (I. Finlay – CIGB, GSK, Chiron, etc.).
- **Recombinant vaccine:** Based on selected-functional menB proteins (Aventis).
- **PolyB – Conjugated vaccines:** NAVA, FDA, Chiron, etc.
- **Mimetic Ag – Vaccines:** Chiron, Finlay-CIGB, etc.

Vaccination Package "Now 2002"

Vaccines against Bacterial Meningitis



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