

Impact of hepatitis B vaccine safety issues on vaccination strategies and their implementation in France

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History of HBV vaccination strategies in France

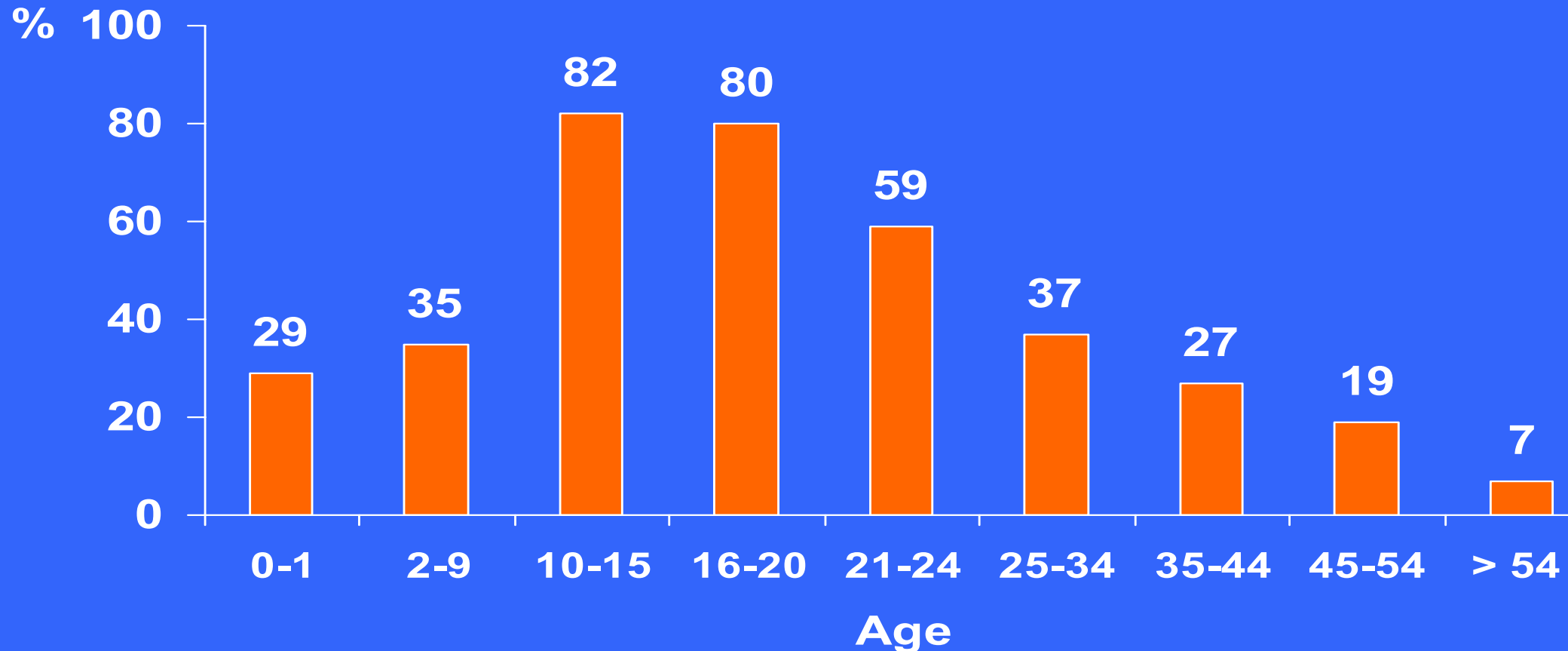
- 1982 : Selective vaccination targeted to high risk groups
- 1992 : Based on North-American experiences showing the inability of selective vaccination to control hepatitis B, World Health Assembly recommendation of “universal” vaccination in all countries
- 1994-1995 : Adoption, in addition to the selective vaccination, of a 2-components vaccination strategy :
 - ⇒ Hep B vaccination included in infant vaccination schedule
 - ⇒ School-based vaccination campaigns for 11 year olds for a ten years period

Implementation of the strategies (1994-1997)

- Infant vaccination : low coverage ($\approx 30\%$)
- Pre-teenagers : high coverage (75 to 80 %)
- High-risk populations : vaccination well beyond the target populations :
 - ⇒ More than 75 millions doses sold by the end of 1997
 - ⇒ More than 84 % of these sales since 1994
 - ⇒ More than 1/3 of the French population vaccinated

Hepatitis B vaccination in France

Coverage according to age - 1998



Vaccine safety data up to March 1998

Increasing number of notifications of adverse events following vaccination to the French Medicine Agency (AFSSAPS), mainly episodes of central demyelination (ECD)

Up to end of 03/98, 249 notifications of ECD (192 first episodes of central demyelination (FECD), 57 MS relapses)

Temporal association between a frequent exposure and a not so rare event in young adults (> 2000 MS/year in 20-49 years) ?

Number of FECD notified in the 2 months following vaccination in 20-44 years old, comparable with the expected number

Difficult to interpret in the context of an under-notification of AE to the AFSSAPS and uncertainty about MS epidemiology

French Drug Agency, September 1998 meeting

Case-control studies

Association between FECD and HB vaccination

- *Pilot study (Hôpital Pitié Salpêtrière, 1997)*
 - OR: 1.8 [0.5 - 6.0] for 2 months interval
 - OR: 1.7 [0.8 - 3.7] all notifications
- *Multi-center study (France, 1998)*
 - OR: 1.4 [0.4 - 4.5] 2 months, documented vaccination
 - OR: 1.8 [0.7 - 4.6] 2 months, all subjects
- *GPRD data base study (UK, 1998)*
 - OR: 1.4 [0.8 - 2.4] 2 months
 - OR: 1.8 [0.6 - 3.9] 2 months

Neither confirm nor disprove a small increase in risk in adult

Number and attributable risk of FECD according to age, under the assumption of a causal relationship with vaccination 1990-1997. Source AFSSAPS/InVS

Age at vaccination	Base-case scenario		Worst-case scenario	
	# of FEDC	Attributable risk per 10 ⁵ vaccinees	# of FEDC	Attributable risk per 10 ⁵ vaccinees
0-1 years	0	0	0	0
2-6 years	0	0	0	0
7-9 years	5	0,23	6	0,84
10-12 years	7	0,08	8	0,27
13-15 years	9	0,19	12	0,77
16 years et plus	135	0,25	161	0,91

Base-case scenario : OR = 1.4 / FEDC, 6/12 following vaccination, 100 % exhaustiveness

Worst-case scenario : OR = 1,8 / FEDC any time since vaccination, 50 % exhaustiveness

Estimated risk of FECD under the assumption of a causal association with HB vaccination and benefits of vaccination for a fictive cohort of 800,000 pre-teenagers followed-up to 35 years of age

	High incidence scenario		Low incidence scenario	
	Best case scenario	Worst case scenario	Best case scenario	Worst case scenario
Number of acute fulminating hepatitis prevented	29	7	12	3
Number of cirrhosis prevented	147	29	58	12
Number of FECD attributable to vaccination	< 2 FECD			

Source : Bulletin épidémiologique hebdomadaire 9/99

Conclusions drawn by InVS - September 1998

In infants : no notification of neurological events following immunization
=> no reason to question the infant vaccination

In adults

⇒ French data do not allow to discard a small excess risk

⇒ Available international data in disfavor of an association

⇒ If a neurological risk exists, it appears negligible for high risk individuals
risk of post-vaccine FEDC < 1/100.000 in adults vs. % of Ag HBs ⊕ ≈
4 to 7 % in HIV ⊕ subjects or STD consultants

For pre-teenagers

⇒ Very few notifications of neurological events following immunization

⇒ Crude risk/benefit analysis not in favor of discontinuation of vaccination

The Minister of Health Press Conference 1st October 1998

- Held in a very emotional context

Hépatite B : les risques de la vaccination

- Une affaire de l'ampleur de celle du sang contaminé risque-t-elle d'éclater bientôt ? La vaccination contre l'hépatite B entraîne des effets secondaires souvent redoutables, dont les cas se multiplient. Or, les patients n'en sont pas avisés...

The Minister of Health Press Conference 1st October 1998

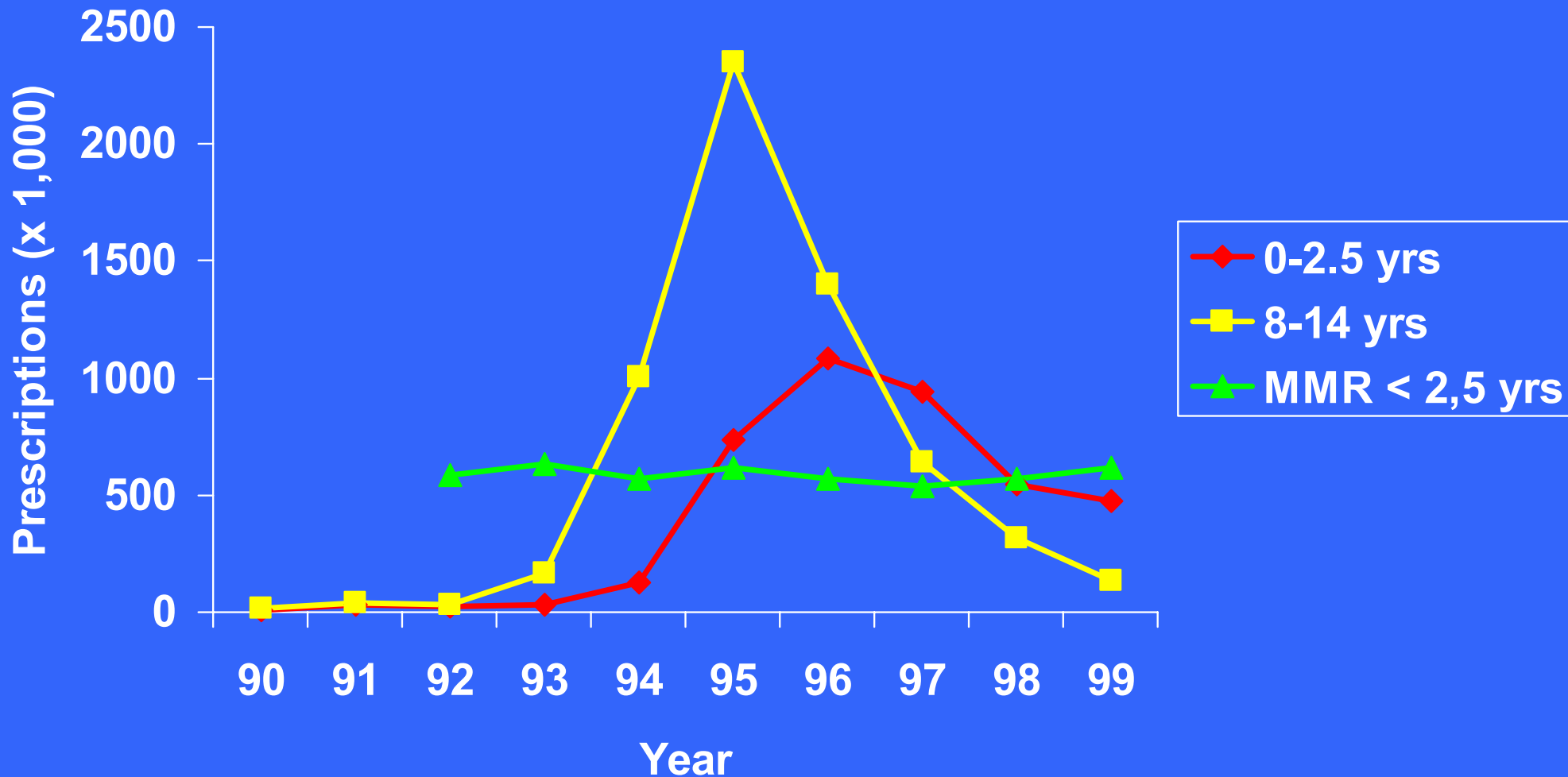
- Held in a very emotional context
- Continuation of the 3 vaccination strategies
- Discontinuation of the school-based campaigns
- Immunization of pre-adolescents possible as individual vaccinations in private practice
- Change for pre-adolescents justified by the need to “better take into account the individual benefits and risks”

Impact of the decision

The discontinuation of school-based campaigns was, up to a certain extent, interpreted as a recognition of a safety issue and created some confusion in media, public and medical community

Continuation of the decrease in vaccination activities as shown by vaccine sales data

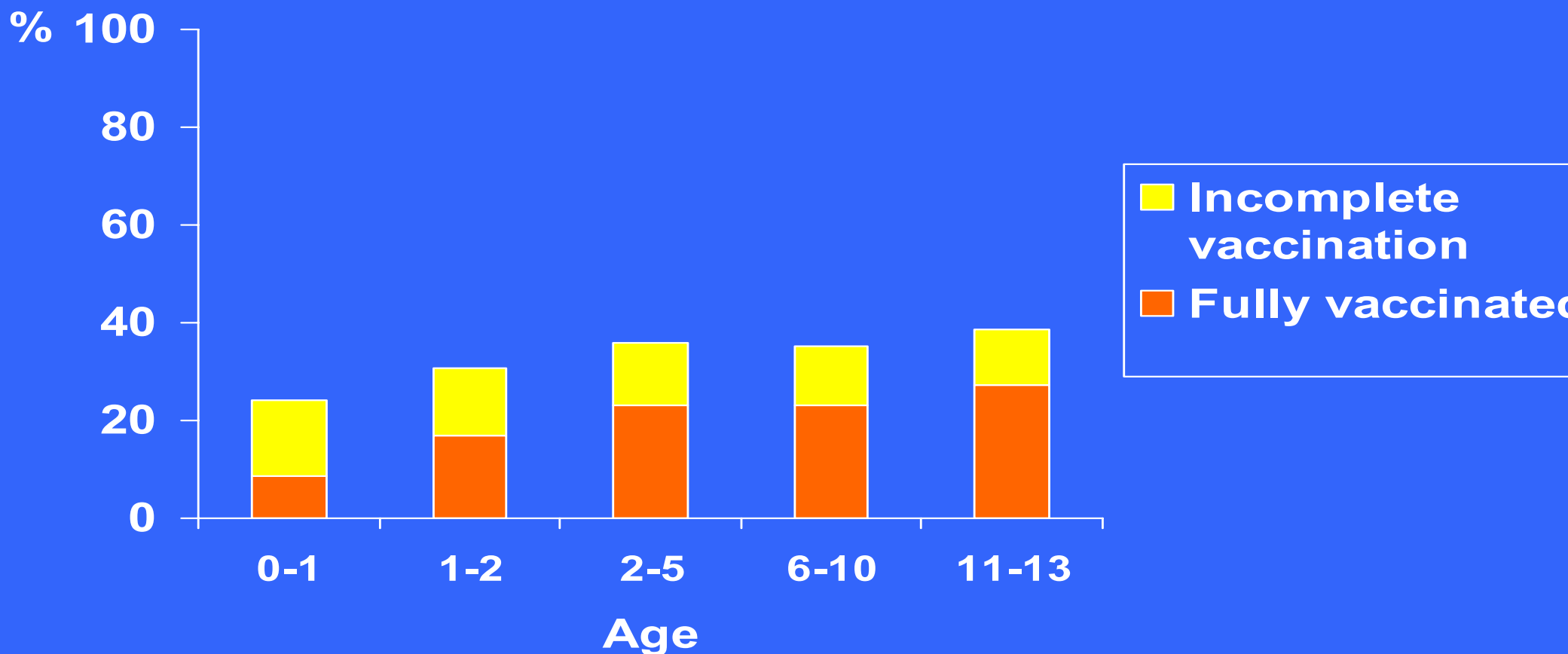
Number of prescribed VHB vaccine doses in the private sector - Infant and pre-adolescent vaccinations, 1990-99



Impact of the decision

- The discontinuation of school-based campaigns was, up to a certain extent, interpreted as a recognition of a safety issue and created some confusion in media, public and medical community
- Continuation of the decrease in vaccination activities as shown by vaccine sales data
- Current low coverage in infants and pre-adolescents
 - ⇒ Coverage at 24 months in 2003 : 28 %
 - ⇒ School health surveys (MoH, Ministry of Education, InVS)
 - 2000 - 01 : 67 % in 14 – 16 years old
 - 2001 - 02 : 30 % in 10 – 11 years old

Hepatitis B vaccination coverage in France according to age - 2002



Impact of the decision

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Continuation of the decrease in vaccination activities as shown by vaccine sales data

Current low coverage in infants and pre-adolescents

Available data in favor of decreasing coverage in high risk populations (except health staff) : new patients in an IVDU clinic: 45 % and 22 % coverage resp. in 1999 and 2001

Position of the various public stakeholders

Expert committees

- Advisory board in immunisation (CTV) has regularly reviewed the data and invariably advised the MOH to maintain the 3-tiered vaccination strategy
- Last statement dated mid-September 2004: “no indication to modify the current recommendations”
- Special ad hoc expert committee set up by the MOH has come up with the same conclusions (Commission Dartigues, 2001)
- Same conclusions reiterated by the jury of the “consensus conference” including some of the best expertise available globally on the topic (September 2003)
- Continuous commitment in favor of vaccination of professional Societies of Hepatology

Position of the various public stakeholders

Ministry of Health

“Available data do not allow to rule out the hypothesis of a weak association...

However, there is no reason to question the current immunisation strategies”

Actually, no change in the immunisation schedule since 1995 (other than discontinuation of the 4 doses schedule and of the booster doses, narrowing of high risk groups definition in 1998)

The 2004 immunization schedule still recommends:

- ⇒ Vaccination of children before 13 years of age
- ⇒ Best done in infancy
- ⇒ Catch-up for pre-teenagers at 11-13 years
- ⇒ Vaccination at any age of high risk subjects
- ⇒ Mandatory vaccination of health professionals