44° CONVEGNO NAZIONALE di Studi di Medicina Trasfusionale
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SIMTI

Epatite B: vaccinazione e donazioni di sangue

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Il sottoscritto Daniele Prati, in qualità di Relatore dichiara che
negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con i soggetti portatori di interessi commerciali in campo sanitario:

- *Macopharma,*
- *Ortho Clinical Diagnostics,*
- *Grifols,*
- *Terumo,*
- *Immucor,*
- *Diamed,*
- *Diatech Pharmacogenetics,*
- *Diasorin.*

Hepatitis B Virus (HBV) vaccination

- WHO estimated that in 2019 only, hepatitis B resulted in 820 000 deaths, mostly from cirrhosis and hepatocellular carcinoma.
- The effective implementation of hepatitis B vaccination programs has resulted in a substantial decrease in the HBV carrier rate and hepatitis B-related morbidity and mortality.
- Several data indicate that HBV vaccination campaigns contributed substantially to decrease the risk of transfusion transmitted HBV, and some countries are expanding indications (in USA, from March 2022 the HBV vaccination is recommended to all adults <60 years old)

Outline

- HBV vaccination: Safety and Efficacy
- How HBV vaccination coverage has contributed to improve the safety of blood transfusion
- Coverage of partners and household contacts of HBV carriers: is vaccination enough to allow blood donations?

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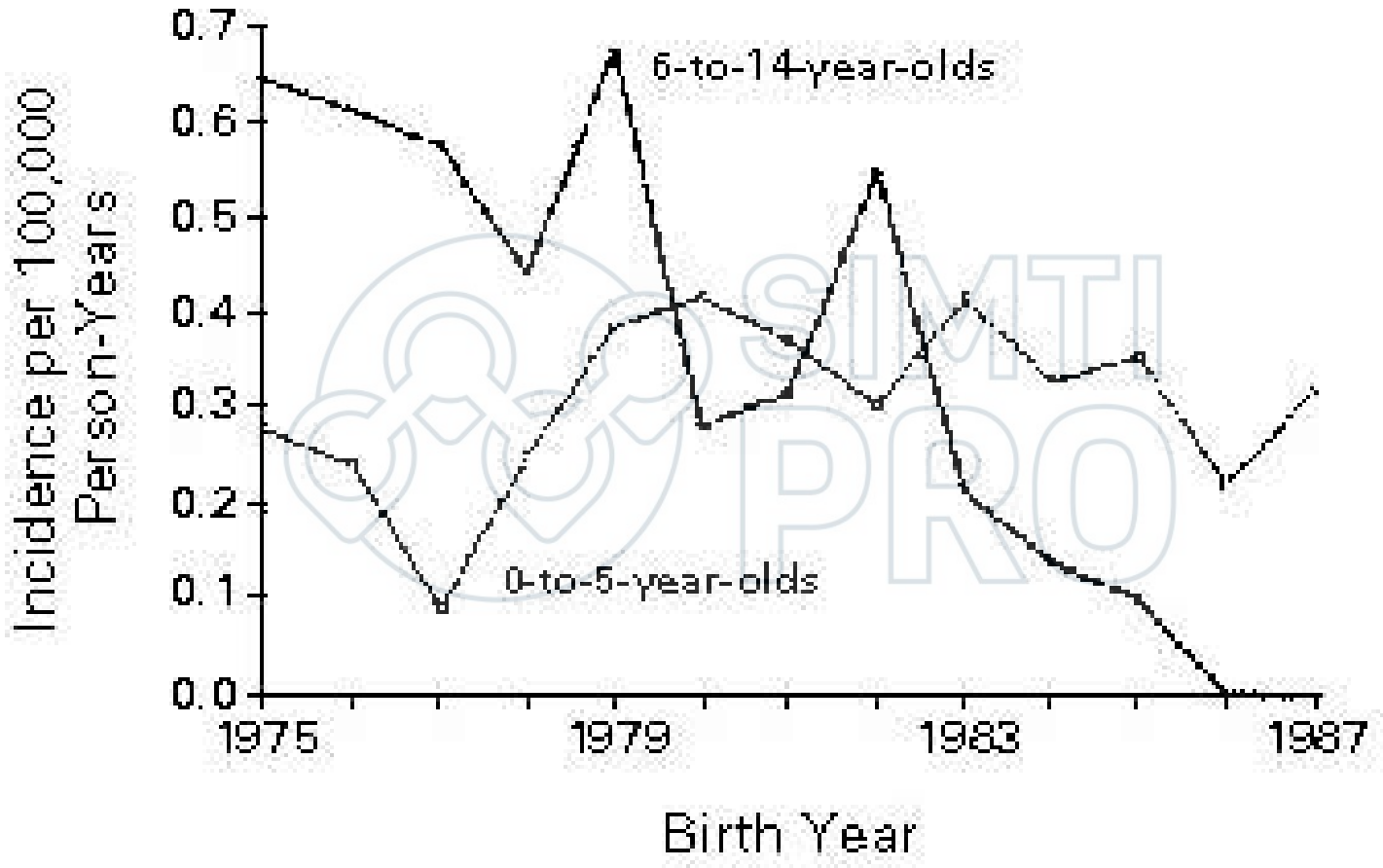
Comparison of the Incidence of Liver Cancer in Children 6 to 14 and 0 to 5 Years of Age, According to Birth Cohort.



Chang M et al. N Engl J Med 1997;336:1855-1859.

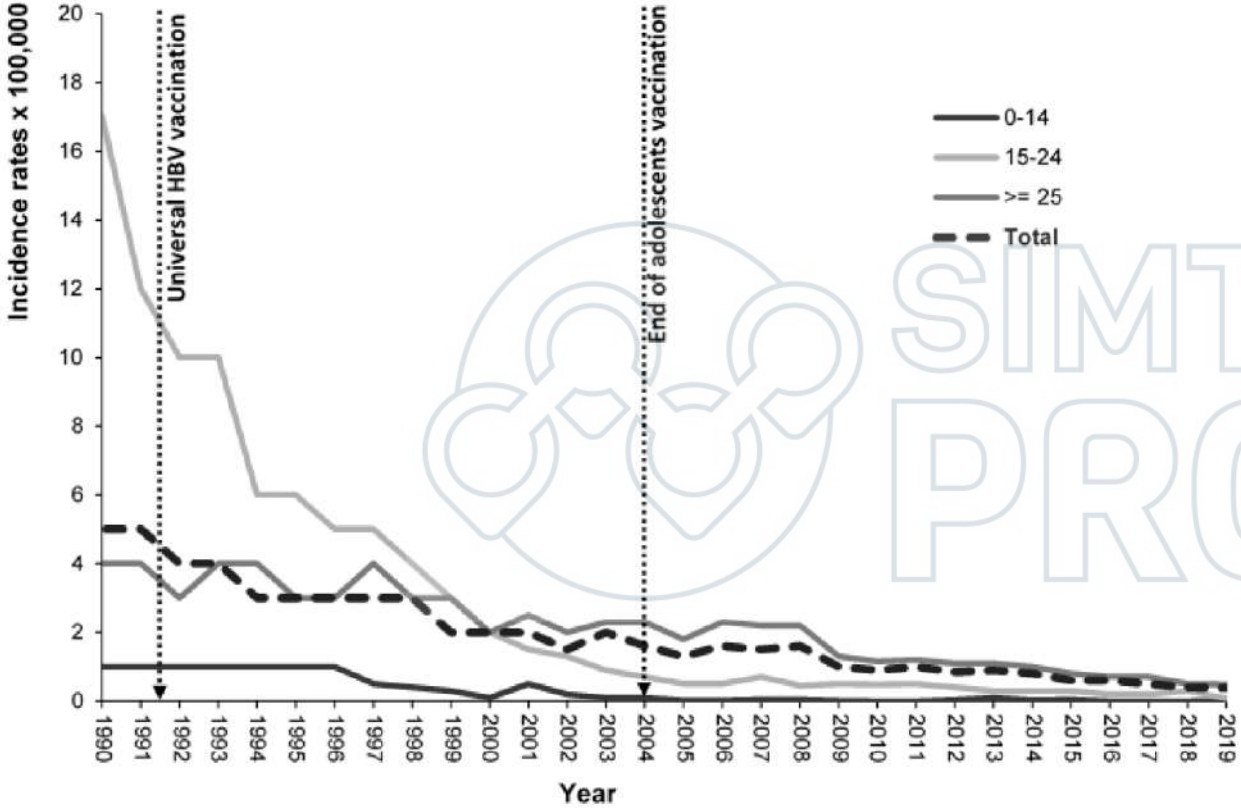
Incidence of acute hepatitis B cases notified in Italy, by age group, SEIEVA

Year	No. of cases per 100,000 persons, by age group				Population surveyed
	0–14 years	15–24 years	⩾25 years	Total	
1991	1	12	4	5.1	16,401,503
1992	1	10	3	4	22,622,762
1993	1	10	4	4	22,622,762
1994	1	6	4	3	22,804,610
1995	1	6	3	3	23,060,981
1996	1	5	3	3	25,900,850
1997	0.5	5	4	3	31,882,134
1998	0.4	4	3	3	31,882,134
1999	0.3	3	3	2	32,331,986
2000	0.1	2	2	2	33,429,357
2001	0.5	1.5	2.5	2	33,429,357
2002	0.2	1.3	2	1.5	33,429,357
2003	0.1	0.9	2.3	2	33,429,357
2004	0.1	0.7	2.3	1.6	33,701,132
2005	0.02	0.5	1.8	1.3	35,194,296

Mele A, Clin Infect Dis, Volume 46, Issue 6, 15 March 2008, Pages 868–875, https://doi.org/10.1086/528687

Effectiveness of Hepatitis B Vaccination Campaign in Italy: Towards the Control of HBV Infection for the First Time in a European Country

Tommaso Stroffolini [1], Filomena Morisco [2], Luigina Ferrigno [3,*], Giuseppina Pontillo [2], Giuseppina Iantosca [3], Valentina Cossiga [2], Simonetta Crateri [3], Maria Elena Tosti [3] and the SEIEVA Collaborating Group



- *In 1991, Italy was the first European country to introduce mandatory HBV vaccination for 3-month-old infants and for 12-year-old children until 2004*
- *As consequence, all subjects <40 years of age are currently vaccinated against HBV*

Legend:

Age groups	Incidence 1990	Incidence 2019	% Reduction 1990–2019
0–14	1.0	0.0	–100.0%
15–24	17.0	0.1	–99.4%
≥25	4.0	0.5	–87.5%
Total	**5.0**	**0.4**	**–92.0%**

2022, 14, 245. https://doi.org/10.3390/v14020245

Hepatitis B Vaccine Safety and Side Effects

- More than 1 billion doses of the hepatitis B vaccine have been given worldwide and it is considered **one of the safest and most effective vaccines ever made**. Numerous studies looking at the vaccine's safety have been conducted by the World Health Organization, U.S. Centers for Disease Control and Prevention, and many different medical societies.
- **No evidence** has been found that the hepatitis B vaccine causes sudden infant deaths (SIDs), autism, multiple sclerosis, or other neurological disorders.
- *Common side effects from the hepatitis B vaccine may include soreness, swelling and redness at the injection site. The vaccine may not be recommended for those with documented yeast allergies or a history of an adverse reaction to the vaccine.*

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Prevalence, incidence and residual risk of transfusion-transmitted hepatitis B virus infection in Italy from 2009 to 2018

Claudio Velati[1,2], Luisa Romanò[3], Ilaria Pati[2], Giuseppe Marano[2], Vanessa Piccinini[2], Liviana Catalano[2], Simonetta Pupella[2], Stefania Vaglio[2], Eva Veropalumbo[2], Francesca Masiello[2], Giulio Pisani[4], Giuliano Grazzini[2,5], Alessandro Zanetti[3], Giancarlo M. Liumbruno[2]

Residual risk is higher in repeat (older, non vaccinated) vs. first time (younger, vaccinated) donors!!

	Estimated n of incident cases[a]	*Person-years*[b]	*Adjusted incidence×10*[5c] *(95% CI)*	*RR×10*[6] *units (95% CI)*	*1: n. units*
Repeat Donors	40	14,700,896	0.408138 (0.28-0.55)	0.193446 (0.14-0.26)	5,169,390
First Time Donors	2	2,723,639	0.110146 (0.01-0.39)	0.051769 (0.004-0.18)	19,316,579
Total Residual Risk				0.169748 (0.11-0.25)	5,891,086

Blood Transfus. 2019

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MINISTERO DELLA SALUTE

DECRETO 2 novembre 2015

Disposizioni relative ai requisiti di qualita' e sicurezza del sangue e degli emocomponenti. (15A09709) (GU Serie Generale n.300 del 28-12-2015 - Suppl. Ordinario n. 69)

- Rapporti sessuali con persone infette o a rischio di infezione da epatite B e C, HIV. Sospensione per 4 mesi dall'ultima esposizione (anche se il donatore è vaccinato per epatite B).
- Convivenza occasionale e/o prolungata abituale con soggetto, non partner sessuale, positivo per HBsAg e/o anti HCV. Sospensione per 4 mesi dalla fine della convivenza e/o dall'ultima esposizione (anche se il donatore è vaccinato per epatite B).

Is this disposition justified, and should we maintain it?

Breakthrough HBV infections

- HBV Infections occurring in individuals who have been successfully vaccinated.
- Clinical breakthroughs with acute or even chronic hepatitis B are very rare . When occur, are typically caused by HBV genotypes different than the vaccine genotypes.
- Much more frequent are breakthroughs which result in asymptomatic-resolving infection that can potentially threaten blood safety:
  - ✓"Chronic" breakthrough infections, OBI-like (HBsAg-, anti-HBc+, sometimes HBV DNA+)
  - ✓ "Recent" breakthrough infections – "HBV DNA+ only" (HBsAg-, anti HBc-, HBVDNA+)

Gerlich WH, Indian J Med Res 2017; McMahon B, Ann Intern Med 2005; Stramer S et al, NEJM 2011)

Antibody Levels and Protection after Hepatitis B Vaccination: Results of a 15-Year Follow-up

Brian J. McMahon, MD; Dana L. Bruden, MS; Kenneth M. Petersen, MD; Lisa R. Bulkow, MS; Alan J. Parkinson, PhD; Omana Nainan, PhD; Marina Khristova, PhD, DSc; Carolyn Zanis, BS; Helen Peters, BS; and Harold S. Margolis, MD

- Prospective cohort study 1578 Alaska Natives (high HBV infection risk) vaccinated at age 6 months or older.
- Over 15 years, breakthrough infections (defined by anti-HBc) were detected in 16 participants
- Breakthroughs occurred more frequently in persons who did not respond to vaccination than those who responded (P 0.01);
- All were asymptomatic. 6/16 had intermittent viremia during follow up.

The NEW ENGLAND JOURNAL of MEDICINE

Nucleic Acid Testing to Detect HBV Infection in Blood Donors

Susan L. Stramer, Ph.D., Ulrike Wend, Daniel Candotti, Ph.D., Gregory A. Foster, B.A., F. Blaine Hollinger, M.D., Roger Y. Dodd, Ph.D., Jean-Pierre Allain, M.D., and Wolfram Gerlich, M.D.

- NAT testing on 3.7 million donations, and further evaluation of those that were HBV DNA–positive but negative for HBsAg and anti-HBc.
- 6 donors who previously vaccinated were positive for HBV DNA, in whom subclinical infection had developed and resolved. Of them, 4 probably acquired HBV infection from a chronically infected sexual partner.
- The breakthrough infections in the vaccinated donors were mostly non-A2 genotype, detectable only by assay of HBV DNA, were clinically asymptomatic, and did not show persistence of HBsAg.

However.....

- Overall, breakthrough infections in fully vaccinated individuals are very rare events.
- The residual risk of post transfusion hepatitis B is very low (~1:6 million units in Italy) and even lower in populations who have higher vaccination coverage *(Velati C, Blood Transfus 2018)* .
- The application of ID-NAT (instead of MP-NAT) for HBV further reduces the risk and is potentially effective in detecting both "chronic" and "recent" breakthrough infections *(Spreafico M, J Hepatol 2015)*
- Even passively administered anti-HBs by concomitant donations from immunized donors protects against donations from OBI donors. *(Candotti D, Gut 2018)*
- Increasing number of HBsAg+ patients are now on antiviral therapy, thus reducing the possibility of breakthrough transmission to vaccinated sexual/household contacts
- In Italy, OBI-like patterns (HBV-DNA positive, HBsAg negative ± anti-HBc) are found almost exclusively in non-vaccinated blood donors *(Spreafico M, J Hepatol 2015).*

Poor efficacy of nucleic acid testing in identifying occult HBV infection and consequences for safety of blood supply in Italy

Marta Spreafico[1,†], Alessandra Berzuini[1], Barbara Foglieni[1], Daniel Candotti[2], Livia Raffaele[1], Irene Guarnori[1], Agostino Colli[3], Francesco Fumagalli Maldini[1], Jean-Pierre Allain[4], Daniele Prati[1,*]

OBI mainly occurs in non vaccinated (older), and transmission is confined to anti-HBs negative

OBI donors	Age	Gender	HBsAg (IU/ml)	Anti-HBs (mIU/ml) [>10]	Anti-HBc	HBc-IgM	Anti-HBe	HBeAg
OBI 1	59	M	Neg	Neg	Pos	Neg	Neg	Neg
OBI 2	45	M	Neg	44	Pos	Neg	Neg	Neg
OBI 3	67	M	Neg	Neg	Pos	Neg	Neg	Neg
OBI 4	65	M	Neg	10	Pos	Neg	Neg	Neg
OBI 5	66	M	Neg	106	Pos	Neg	Neg	Neg
OBI 6	41	M	Neg	Neg	Pos	Neg	Pos	Neg
OBI 7	48	M	Neg	40	Pos	Neg	Neg	Neg
OBI 8	36	M	Neg	245	Pos	Neg	Pos	Neg
OBI 9	51	M	Neg	137	Pos	Neg	Neg	Neg
OBI 10	66	M	Neg	Neg	Pos	Neg	Neg	Neg
OBI 11	45	M	Neg	Neg	Neg	Neg	Neg	Neg
OBI 12	27	M	Neg	49	Neg	Neg	Neg	Neg
OBI 13	52	M	Neg	33	Neg	Neg	Neg	Neg
OBI 14	62	M	Neg	36	Pos	Neg	Neg	Neg
OBI 15	65	M	Neg	17	Pos	Neg	Neg	Neg
OBI 16	62	M	Neg	128	Pos	Neg	Neg	Neg
OBI 17	48	M	Neg	43	Pos	Neg	Pos	Neg
OBI 18	64	M	Neg	172	Pos	Neg	Pos	Neg

Spreafico M, J Hepatol 2015

Deferral policy for partners/family members of HBsAg carriers, independently from vaccination

Time for reappraisal?

Current policy in Europe

a survey promoted by CNS within European Blood Alliance (EBA)

What is your policy regarding candidate blood donors who admit sexual contacts with patients who have hepatitis B?

23 countries/blood donor organizations answered to the poll:

- 19 from EBA,
- 4 from the *Alliance of Blood Operators* (ABO)

Current policy in other countries

a survey promoted by CNS within European Blood Alliance (EBA)

	Permanent deferral	Temporary deferral since last contact[1]	Decision based on individual risk assessment[2]
Sexual partners	1 country (Croatia)	10 countries/organizations (Denmark, Ireland, Latvia, Portugal, Sweden, Switzerland, Norway, Ireland, Northern Ireland, American Red Cross)	10 countries/organizations (Finland, France, Luxembourg, Malta, Slovenia, England, Wales, Australian Red Cross, Canadian Blood Services, Vitalant USA)
Household contacts	--	9 countries/organizations (Croatia, Denmark, Estonia, Ireland, Latvia, Portugal, Sweden, Switzerland, American Red Cross)	12 countries/organizations (Finland, France, Luxembourg, Malta, Norway, Slovenia, Northern Ireland, England, Wales, Australian Red Cross, Canadian Blood Services, Vitalant USA)

[1] Time since last contact varies (3-12 months);

[2] Takes into account immunity/vaccination status, presence of anti-HBs, type of contact, virological status of the contact

Summary and conclusions

- HBV vaccination in Italy: a success story
- Positive impact on blood safety
- Extension of vaccination indications to older ages would also be beneficial.
- The current temporary deferral for sexual partners and household contacts of HBsAg carriers often translates into lifetime ban from donations.
- Actually, breakthrough infections remain a theoretical threat in terms of transfusion transmission, but ovarall risk is likely negligible.
- Thus, a revision of the current donation policy might be opportune, shifting towards an individual risk assessment taking into account vaccination status, as already done in several other resource rich countries.
- This would allow to increase the donor pool, contribute to tackle hepatitis B infection stigma and reduce vaccine hesitancy.