PE37/ 36

Long term response to mandatory anti-HBV vaccination: risks for disease acquisition and opportunities for re-vaccination within the ICONA cohort.

Roberto Rossotti[1], Annalisa Saracino[2], Patrizia Lorenzini[3], Chiara Alcantarini[4], Alessandra Latini[5], Giuseppe Lapadula[6], Silvia Nozza[7], Loredana Sarmati[8], Enrico Girardi[3], Antonella Castagna[7], Antonella d'Arminio Monforte[9], Massimo Puoti[1] on behalf of the ICONA Foundation Study Group.

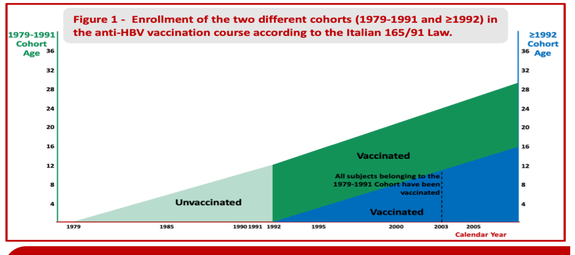
1 ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy ~ 2 University of Bari, Bari, Italy ~ 3 INMI L. Spallanzani, Rome, Italy ~ 4 University of Turin – Department of Medical Sciences, Turin, Italy ~ 5 San Gallicano Dermatological Institute, Rome, Italy ~ 6 University of Milano Bicocca, Monza, Italy ~ 7 San Raffaele Scientific Institute, Milan, Italy ~ 8 University of Rome Tor Vergata, Rome, Italy ~ 9 University of Milan – San Paolo Hospital, Milan, Italy.

EACS European AIDS Clinical Society
17th EUROPEAN AIDS CONFERENCE
November 6–9, 2019 | Basel, Switzerland

BACKGROUND

- Italy was traditionally considered a Country with an intermediate prevalence for HBV infection, with HBsAg positivity ranging between 1.6 and 3.4% (with areas topping to 5.6%).
- HBV incidence and prevalence started to decrease during the 1980s for the improvement of socio-economic conditions, the change in medical procedures, a better knowledge of local transmission routes and the availability in 1983 of a vaccine for key populations such as intravenous drug users (IVDU), men who have sex with men (MSM), patients undergoing hemodialysis and healthcare workers.
- In 1991, the law n. 165 introduced mandatory HBV vaccination for all people born after 1979 through two different cohorts (**Figure 1**):
  - Born between 1979 and 1991: vaccinated at their 12th birthday;
  - Born after 1992: vaccinated at their 1st birthday.
- The rate of vaccination response is generally 90 to 95%, but 20 years after vaccine administration the coverage drops to 60%.
  - In adult HIV-positive individuals who received the vaccination after HIV infection, the response rate is below 30% seven years after vaccine administration.
- According to the Ministry of Health, vaccination coverage in Italy has always been around 95%.

Figure 1 - Enrollment of the two different cohorts (1979-1991 and ≥1992) in the anti-HBV vaccination course according to the Italian 165/91 Law.



AIMS

- Aims of present Study are:
  - Assess long term vaccination response in Italian horizontally infected HIV+ subjects who received compulsory anti-HBV vaccine in their childhood;
  - Evaluate the proportion and risk factors for HBV acquisition despite vaccination.

STUDY DESIGN AND METHODS

STUDY POPULATION

- ICONA Foundation Cohort is an observational Study that enrolls HIV positive subjects naïve to antiretroviral treatment from more than 50 Centers operating throughout Italy. Since 1997, more than 16,500 individuals have been included in the ICONA Study.
- Subjects born in Italy after 1979 with full serology for HBV available at ICONA enrollment (i.e. before antiretroviral treatment start) were included.
- Demographic, clinical and behavioral features were collected.

STATISTICAL ANALYSIS

- Factors associated to maintaining protective anti-HBs levels (>10 IU/mL) were analyzed.
- Cumulative incidence of any infection (HBsAg+, anti-HBs+/anti-HBc+, or anti-HBs-/anti-HBc+) at enrollment were evaluated by means of logistic regression.
- Follow up was calculated as the interval between time of vaccination completion and date of performance of serology.

RESULTS (1)

- 1,628 individuals were included: 88.7% males with a median age of 29 years (IQR 25-32) mainly belonging to the 1979-1991 cohort (**Table 1**).

Table 1 - Demographic, clinical and behavioral features of study population.

		N=1,628	%			N=1,628	%
Gender, Male		1,444	88.7	Non-AIDS malignancies in previous clinical history		66	4.1
Year of birth	1979-1991	1,465	89.9	CD4 cell count at baseline	<200	216	13.3
	≥1992	163	10.1		200-350	320	20.0
Mode of HIV transmission	Heterosexual	348	21.4		>350	1,037	63.7
	IVDU	76	4.7		Missing	55	3.4
	MSM	1,128	69.3	HIV RNA at baseline	<100k	1,022	62.8
	Other/Unknown	76	4.7		100k-500k	342	21.0
BMI	<18.5	62	3.8		>500k	173	10.6
	18.5-25	891	54.7		Missing	91	5.6
	25-30	169	10.4	CDC C stage		72	4.4
	>30	30	1.8	HCV-Ab positive		78	4.8
	Missing	476	29.2	Active smokers		742	45.6
Geographic area of residency	North	763	47.3	Alcohol use	Abstainer	536	32.9
	Center	562	34.9		Occasional	573	35.2
	South	287	17.8		Daily	88	5.4
Any STI in previous clinical history		235	14.4		Missing	431	26.5

IVDU: intra-venous drug users; MSM: men who have sex with men; BMI: body mass index; STI: sexually transmitted infection.

RESULTS (2)

- 1,145 subjects showed a protective anti-HBs value >10 IU/mL: thus, 70.3% resulted vaccine responder after a mean follow up of 18.1 years.
- 483 individuals did not show a protective anti-HBs value:
  - 393 (24.2%) resulted negative for HBsAg, anti-HBs and anti-HBc, thus they could be eligible for re-vaccination;
  - 90 (5.5%) showed a serology consistent with a contact with HBV before ICONA enrollment:
    - 12 (0.7%) were HBsAg+ → chronic infection;
    - 66 (4.1%) were anti-HBs+/anti-HBc+ → previous infection;
    - 12 (0.7%) presented an isolated anti-HBc → occult infection (also defined as "Phase 5" in the 2017 EASL Guidelines).

Table 2 - Factors associated with response to anti-HBV vaccination and persistence of anti-HBs value >10 IU/mL.

Univariate		OR	95%CI		p	Multivariate		OR	95%CI		p
Year of birth	1979-1991	1.00				Year of birth	1979-1991	1.00			
	≥1992	**0.51**	**0.36**	**0.71**	**0.000**		**≥1992**	**0.47**	**0.34**	**0.66**	**0.000**
Female gender *versus* male		**0.67**	**0.49**	**0.92**	**0.014**	Female gender *versus* male		0.78	0.52	1.16	0.220
Mode of HIV transmission	Heterosexual	**0.72**	**0.56**	**0.93**	**0.012**	Mode of HIV transmission	Heterosexual	0.78	0.56	1.07	0.126
	IVDU	0.79	0.48	1.30	0.362		IVDU	0.85	0.51	1.42	0.526
	MSM	1.00					MSM	1.00			
	Other	1.09	0.64	1.85	0.749		Other	1.19	0.69	2.03	0.534
CDC C Stage		**0.65**	**0.40**	**1.06**	**0.082**	CDC C Stage		0.71	0.13	3.99	0.698
Non-AIDS defining malignancies		**0.64**	**0.38**	**1.05**	**0.080**	Non-AIDS defining malignancies		0.76	0.13	4.55	0.765
Previous STI		0.88	0.66	1.19	0.415						
HCV-Ab	Negative	1.00									
	Positive	0.79	0.49	1.27	0.325						
	Missing	0.92	0.43	1.95	0.818						
Nadir CD4	<200	0.87	0.64	1.20	0.398						
	200-350	1.14	0.86	1.51	0.364						
	>350	1.00									
	Missing	0.68	0.39	1.19	0.173						
HIV RNA at baseline	<100k	1.00				HIV RNA at baseline	<100k	1.00			
	100k-500k	**0.78**	**0.60**	**1.01**	**0.062**		**100k-500k**	**0.78**	**0.59**	**1.01**	**0.064**
	>500k	1.21	0.83	1.75	0.315		>500k	1.33	0.91	1.95	0.147
	Missing	0.74	0.47	1.16	0.186		Missing	0.76	0.48	1.21	0.245

- None of the HIV-related and behavioral features resulted associated with response to anti-HBV vaccination;
  - Belonging to the 1979-1991 cohort resulted the only factor associated to anti-HBs level >10 IU/mL.
- Over the course of 29,343 years, cumulative incidence of any HBV infection (chronic, previous, occult) of the was 3 per 1000 patients/years of follow up (PYFU, 95%CI 2.5-3.7).

Table 3 - Factors associated with HBV acquisition before ICONA enrollment.

Univariate		OR	95%CI		p	Multivariate		OR	95%CI		p
Year of birth	1979-1991	1.00									
	≥1992	0.75	0.34	1.64	0.469						
Mode of HIV transmission	Heterosexual	1.16	0.70	1.94	0.563						
	IVDU	1.55	0.65	3.72	0.324						
	MSM	1.00									
	Other	1.01	0.36	2.85	0.990						
CDC C stage		**2.25**	**1.04**	**4.84**	**0.039**	CDC C stage		2.08	0.86	5.01	0.104
Previous STI		1.00	0.55	1.83	0.998						
HCV-Ab	Negative	1.00				HCV-Ab	Negative	1.00			
	Positive	**3.16**	**1.60**	**6.23**	**0.001**		**Positive**	**2.77**	**1.35**	**5.72**	**0.006**
	Missing	2.75	0.94	8.04	0.065		**Missing**	**3.30**	**1.10**	**9.90**	**0.034**
Nadir CD4	**<200**	**1.65**	**0.95**	**2.88**	**0.075**	Nadir CD4	<200	1.55	0.82	2.93	0.175
	200-350	0.90	0.50	1.61	0.711		200-350	0.88	0.49	1.60	0.684
	>350	1.00					>350	1.00			
	Missing	1.05	0.32	3.47	0.936		Missing	0.56	0.15	2.09	0.386
Smoking	No	1.00				Smoking	No	1.00			
	Yes	**2.03**	**1.25**	**3.29**	**0.004**		**Yes**	**1.89**	**1.13**	**3.14**	**0.015**
	Missing	**2.18**	**1.08**	**4.43**	**0.030**		**Missing**	**2.37**	**1.02**	**5.47**	**0.044**
Alcohol use	Abstainer	1.00				Alcohol use	Abstainer	1.00			
	Occasional	1.13	0.66	1.95	0.662		Occasional	0.99	0.56	1.74	0.974
	Daily	**3.23**	**1.56**	**6.69**	**0.002**		**Daily**	**2.55**	**1.19**	**5.44**	**0.016**
	Missing	1.15	0.64	2.06	0.633		Missing	0.84	0.43	1.61	0.590

- Being HCV co-infected, smoker and daily alcohol user are risk factors for HBV infection before ICONA enrollment;
  - None of HIV-related features resulted associated with HBV acquisition.

CONCLUSIONS

- **Giving a long-term vaccine efficacy of 60% and a national vaccination coverage ranging between 93.0 and 96.5%, in the general population the expected response rate is 57% (CI 55.8-57.9%): thus, the rate of responders in HIV-positive subjects (70.3%) looks at least comparable.**
- **The reasons for non-response are not clear: sex, age, BMI, smoking, previous oncologic diseases and certain HLA patterns have been associated with a lack of protective anti-HBs. In HIV-positive subjects, previous AIDS-defining events and virologic and immunologic conditions are additional factors related to vaccine non-response. Nevertheless, our data — from a larger cohort and with a longer follow up of what reported in literature — do not support these observations.**
- **A US study performed in a hyperendemic population after mass vaccination found a cumulative incidence of HBV infection of 0.74 (CI 95% 0.31-1.45) per 1000 PYFU. In our study population, cumulative incidence looks higher underlying the elevated risky condition of HIV-infected individuals.**
- **Around 25% of individuals who were vaccinated in their infanthood are still susceptible to HBV infection, hence they should be identified and undergo re-vaccination as soon as possible.**

Acknowledgments – Icona Foundation Study Group

BOARD OF DIRECTORS: A d'Arminio Monforte (President), A Antinori (Vice-President), M Andreoni, A Castagna, F Castelli, R Cauda, G Di Perri, M Galli, R Iardino, G Ippolito, A Lazzarin, GC Marchetti, G Rezza, F von Schloesser, P Viale.
SCIENTIFIC SECRETARY: A d'Arminio Monforte, A Antinori, A Castagna, F Ceccherini-Silberstein, A Cozzi-Lepri, E Girardi, S Lo Caputo, C Mussini, M Puoti, CF Perno. **STEERING COMMITTEE**: A Antinori, F Bai, C Balotta, A Bandera, S Bonora, M Borderi, A Calcagno, A Capetti, MR Capobianchi, A Castagna, F Ceccherini-Silberstein, S Cicalini, A Cingolani, P Cinque, A Cozzi-Lepri, A d'Arminio Monforte, A Di Biagio, E Girardi, N Gianotti, A Gori, G Guaraldi, G Lapadula, M Lichtner, S Lo Caputo, G Madeddu, F Maggiolo, G Marchetti, L Monno, C Mussini, S Nozza, CF Perno, C Pinnetti, M Puoti, E Quiros Roldan, R Rossotti, S Rusconi, MM Santoro, A Saracino, L Sarmati. **STATISTICAL AND MONITORING TEAM**: A Cozzi-Lepri, I Fanti, L Galli, P Lorenzini, A Rodano', M Macchia, A Tavelli. **BIOLOGICAL BANK INMI**: F Carletti, S Carrara, A Di Caro, S Graziano, F Petroni, G Prota, S Truffa.
PARTICIPATING PHYSICIANS AND CENTERS: Italy A Giacometti, A Costantini, V Barocci (Ancona); G Angarano, L Monno, E Milano (Bari); F Maggiolo, C Suardi (Bergamo); P Viale, V Donati, G Verucchi (Bologna); F Castelnuovo, C Minardi, E Quiros Roldan (Brescia); B Menzaghi, C Abeli (Busto Arsizio); B Cacopardo, B Celesia (Catania); J Vecchiet, K Falasca (Chieti); A Pan, S Lorenzotti (Cremona); L Sighinolfi, D Segala (Ferrara); P Blanc, F Vichi (Firenze); G Cassola, C Viscoli, A Alessandrini, N Bobbio, G Mazzarello (Genova); M Lichtner, L Fondaco, (Latina); P Bonfanti, C Molteni (Lecco); A Chiodera, P Milini (Macerata); G Nunnari, G Pellicanò (Messina); A d'Arminio Monforte, M Galli, A Lazzarin, G Rizzardini, M Puoti, A Castagna, ES Cannizzo, MC Moioli, R Piolini, D Bernacchia, S Salpietro, C Tincati, (Milano); C Mussini, C Puzzolante (Modena); C Migliorino, G Lapadula (Monza); V Sangiovanni, G Borgia, V Esposito, G Di Flumeri, I Gentile, V Rizzo (Napoli); AM Cattelan, S Marinello (Padova); A Cascio, M Trizzino (Palermo); D Francisci, E Schiaroli (Perugia); G Parruti, F Sozio (Pescara); G Magnani, MA Ursitti (Reggio Emilia); M Andreoni, A Antinori, R Cauda, A Cristaudo, V Vullo, R Acinapura, D Moschese, M Capozzi, A Mondi, A Cingolani, M Rivano Capparuccia, G Iaiani, A Latini, R Gagliardini, MM Plazzi, G De Girolamo, A Vergori (Roma); M Cecchetto, F Viviani (Rovigo); G Madeddu, A De Vito(Sassari); B Rossetti, F Montagnani (Siena); A Franco, R Fontana Del Vecchio (Siracusa); C Di Giuli (Terni); P Caramello, G Di Perri, S Bonora, GC Orofino, M Sciandra (Torino); M Bassetti, A Londero (Udine); V Manfrin, G Battagin (Vicenza); G Starnini, A Ialungo (Viterbo).

References

- D'Argenio P, et al. Public Health 1989.
- D'Amelio R, et al. Eur J Epidemiol 1994.
- McMahon BJ, et al. JID 2009.
- Lara AN, et al. Vaccine 2017.
- Nicolini LA, et al. AIDS Res Hum Retrov 2018.
- http://epicentro.iss.it/temi/vaccinazioni/dati_Ita.asp#epb

Funding

ICONA Foundation is supported by unrestricted grants from BMS, Gilead Sciences, Janssen, MSD and ViiV Healthcare.

Contact Information

Mail: Roberto.rossotti@ospedaleniguarda.it

Address: ASST Grande Ospedale Metropolitano Niguarda, piazza Ospedale Maggiore 3, 20162, Milan, Italy.