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Placebo Controlled Pneumococcal Immunization in Patients with Bronchogenic Carcinoma*

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Abstract—*Pneumococcal vaccine [heptadecavalent types* 1, 2, 3, 4, 6*A*, 7*F*, 8, 9*N*, 11*A*, 12*F*, 14, 15*F*, 17*F*, 18*C*, 19*F*, 23*F and* 25 *pneumococcal capsular polysaccharide vaccine (Moniarix^R)] or placebo were evaluated in* 26 *and* 21 *patients with bronchogenic carcinoma, most of whom did not receive prior radiotherapy or chemotherapy. No difference was detected as far as clinical outcome is concerned:* 3 *vaccinated patients out of* 26 (11.5%) *developed pneumococcal infections* (1 *fatal bacteremia*) *and* 4/21 (19%) *of those who received a placebo presented such an infection* (1 *fatal bacteremia*).

The antibody response was significantly increased in the vaccinees for types 1, 2, 7*F*, 8, 9*N*, 12*F*, 14, 17*F*, 18*C*, 23*F and* 25.

INTRODUCTION

PNEUMOCOCCI are important pathogens in the general population but their role in cancer patients has been less often appreciated. Sixty cases of pneumococcal bacteremia, observed at the Sloan-Kettering Memorial Cancer Center, New York, between 1955 and 1971 have been reported by Folland *et al.* [1]; in their series, patients with leukemia and lymphoma were found to be particularly susceptible, and despite appropriate treatment, 53% of the patients died. More recently, Kilton *et al.* reported 14 patients with cancer and pneumococcal bacteremia, 5 of whom died in spite of what appeared active antimicrobial therapy [2].

In our experience at the Institut Bordet we found pneumococcal bacteremia to be 6 times less frequent than gram negative bacillary sepsis [3]. Patients with chronic lymphocytic leukemia and those with bronchogenic carcinoma were particularly predisposed to pneumococcal infection. In addition, we observed a high rate of mortality (42%) in spite of antimicrobial therapy that was effective *in vitro*; among 10 patients who died within 3 days after onset of treatment, 8 had received 'adequate' antimicrobials.

This is the reason why we undertook a controlled study of pneumococcal immunization in patients with bronchogenic carcinoma. Most studies in the field of pneumococcal vaccination in cancer patients have dealt primarily with the antibody response [4]. It was found, overall, that the time of vaccination was important and should precede splenectomy, chemotherapy or radiotherapy; in these studies, the antibody response was frequently found impaired, especially if vaccination took place after chemotherapy.

MATERIAL AND METHODS

All the 50 patients included in this series had histologically proven bronchogenic carcinoma. Three were lost for follow-up and will no longer be considered here. The characteristics of our patients are summarized in Table 1. The two groups were comparable. It should be remarked that most patients did not receive radiotherapy or chemotherapy prior to immunization.

The vaccine was provided by Smith Kline and French Laboratories in numbered boxes, prepared according to prior randomization. The vaccine consisted of a monodose vial containing the purified polysaccharides dissolved in a sterile 0.9% sodium chloride solution containing 0.25% phenol; and the placebo of a sterile 0.9% sodium chloride solution containing 0.25% phenol. The two preparations looked identical.

The immunization was performed at the first visit of the patient to the Institut Bordet. The following technique was employed: the vaccine or the placebo was administered subcutaneously in

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Table 1. Characteristics of the patients

	Vaccine (VA)	Placebo (PL)
No. of patients	26	21
Male/female ratio	25/1	20/1
Mean age (range)	60 (42–76)	62 (45–78)
Non small cell lung cancer	19	21
Small cell lung cancer	7	0
Limited disease	14	8
Disseminated disease	12	13
Time between immunization and therapy (days)		
Median	5	4
Mean	8,7	6,7
Therapy prior VA/PL		
No prior therapy	16	11
Surgery	2	3‡
Radiotherapy	5	6
Chemotherapy*	3	1
Therapy after VA/PL		
No further therapy	4	3
Radiotherapy	11	11
Chemotherapy†	11	7

* Among VA patients: pepbleomycin followed by cisplatin + VP 16 + vindesine (1); cisplatin + VP 16 (1); deoxydoxorubicin (1). Among PL patients, cisplatin + VP 16 (1).

† NSCLC patients received cisplatin + VP16; SCLC received adriamycin + VP16 + cyclophosphamide with or without cisplatin

‡ 2 patients received RXT after surgery

the region of the deltoid muscle to all subjects. No adverse reactions to the administration of the vaccine or the placebo were noticed.

Blood was obtained from all patients, just prior to the administration of the vaccine or placebo; serum was stored at −20°C until used. A second specimen of blood could be obtained from 17 vaccinees and 12 patients who received the placebo. The median time elapsed between the 2 blood collections was 15 days in the vaccinees and 15 in the placebo recipients. So the time between the two blood collections has no influence on the rate of antibodies.

The assay for pneumococcal antibodies was performed by Smith Kline and French Laboratories using a radioimmunoassay. Results were expressed as nanograms of N2. Statistical analysis was performed using the non parametric tests of Mann–Whithey with the SPSS program on the CDC 750 computer at Brussels University.

Assessment of the neoplastic disease in the patients included in this series was made according to the current protocols used by the EORTC Lung Cancer Working Party [5,6].

All patients were followed closely at the outpatient clinic; all patients with febrile episodes or new chest complaints were hospitalized for extensive work-up. Chest X-rays were obtained in all cases as well as blood cultures and cultures of bronchial secretions that were expectorated or obtained by bronchial aspiration or lavage performed by fiberoptic bronchoscopy. Other potential sites of infections were cultured as well. These specimens were handled by the routine microbiology laboratory, but with a special attention to the isolation of pneumococci. Isolates were not serotyped.

Pneumococcal infections were defined as febrile episodes associated with pneumococci in pure or preponderant culture from a likely clinical site, i.e. upper or lower respiratory tract secretions; and/or with positive blood cultures for pneumococci.

RESULTS

As indicated in Table 2, no differences were observed here between the recipients of the vaccine or the placebo as far as pneumococcal infections and deaths related to these infections are concerned. Pneumococcal bronchopneumonia was diagnosed in 2 and pneumococcal pansinusitis in 1, out of 26 vaccinated patients (11.5%); pneumococcal bronchopneumonia was diagnosed in 4/21 (19%) of those who received the placebo. One patient with bronchopneumonia, in each group had documented bacteremia; these two patients died respectively within 1 and 2 days after onset of therapy. The other patients survived for more than 2 weeks after the infection.

In addition, one patient died with pneumococcal bronchopneumonia 2 days after vaccination; he is not considered as a failure of the immunization procedure.

Table 3 summarizes the characteristics of the seven (14.8%) patients who presented with pneumococcal infections in this series. Five had non small cell lung cancer and six presented with a disseminated neoplastic disease. Four were receiving radiotherapy and four chemotherapy at the time of the infection. The delay between immunization and the onset of the infection was relatively short: 15–62 days. With the exception of the two bacteremic patients who died soon after the onset of infection, the other patients survived for 15–350+ days after the onset of pneumococcal

Table 2. Pneumococcal infections and related mortality in vaccinated and non-vaccinated patients with bronchogenic carcinoma

	Vaccine	Placebo
Total No. of patients	26	21
No. pneumococcal infections*	3 (11.5%)†	4 (19.0%)
No. pneumococcal septicemias‡	1 (3.8%)	1 (4.7%)
No. deaths from pneumococcal infection‡	1 (3.8%)	1 (4.7%)

* All were bronchopneumonias except one patient with pansinusitis†.

‡ The two septicemias complicated bronchopulmonary infections: both were fatal.

Table 3. Patients with bronchogenic carcinoma having developed pneumococcal infection after vaccine or placebo

Patients	VA/PL	Age	Sex	Cancer	LD/DD	Therapy for cancer Before VA/PL	Therapy for cancer After VA/PL	Interval of time VA/PL Infection (days)	Survival after onset of infection (days)	Cause of death (+)
DEZ...	PL	56	M	NSCLC	DD	none	RXT	24 (pneumonia)	40	Cancer
CAN...	PL	56	M	NSCLC	DD	none	RXT, CT	20 (bacteremia) (pneumonia)	2	Sepsis
CAT...	PL	53	M	NSCLC	DD	surgery+RXT	RXT	15 (pneumonia)	15	Cancer
MAE...	PL	75	M	NSCLC	DD	none	RXT	15 (pneumonia)	30	Pulmonary superinfection
CHI...	VA	52	M	SCLC	DD	CT+RXT	CT	13 (bacteremia) (pneumonia)	1	Sepsis
PED...	VA	57	M	NSCLC	LD	RXT	CT	62 (pneumonia)	59	Pulmonary hemorrage
VAN...	VA	61	M	SCLC	DD	none	CT	21 (sinusitis)	350+	Alive

PL: placebo; VA: vaccine; M: male; NSCLC: non small cell lung cancer; SCLC: small cell lung cancer; LD: limited disease; DD: disseminated disease; RXT: radiotherapy; CT: chemotherapy.

infection. Three died as a result of progressive neoplastic disease and one from a pulmonary superinfection caused by a multi-resistant strain of *S.aureus* that appeared on day 21 after the onset of the pneumococcal bronchopneumonia which had been successful treated with penicillin G.

Tables 4 and 5 indicate the levels of pneumococcal antibodies in 12 patients who received the placebo and in 17 patients who received the vaccine. The initial antibody levels prior to the administration of the placebo or the vaccine were not significantly different in these two groups. On the other hand, a significant increase of the level of antibodies after the vaccination were detected for the following antigens: 1, 2, 7F, 8, 9N, 12F, 14, 17F, 18C, 23F and 25. The mean increase in antibodies for these antigens is indicated in Table 6; it can be seen that the antibody response was very different in magnitude depending on the various serotypes. The mean increase was less than four-fold for types 1, 2, 3, 4, 6A, 7F, 8, 12F, 17F and 25.

Overall, no correlation between the levels of antibodies and the type of therapy given before or after vaccination was found. However, only a few patients with each therapeutic modality could be evaluated for antibody response. Patients without pretreatment who received radiotherapy after vaccination (seven patients) had a significantly increased antibody response for antigens No. 2, 14, 25 ($P = 0.03$) as compared to four patients who received chemotherapy less than 10 days after vaccination. Similarly, antibody response to antigen No. 14 and 25 was significantly increased in six patients who received chemotherapy more than 10 days after the vaccination as compared to four patients who received chemotherapy earlier.

DISCUSSION

We have failed to find a difference between the clinical outcome of patients with bronchogenic carcinoma who received a polyvalent vaccine or a placebo in spite of a significant increase of antibody levels in the vaccinees; however, for many common pneumococcal types the rise of antibody was modest. No clear relationship between antibody response and the type of therapy given prior to or after vaccination could be detected although only few patients could be adequately studied.

The evaluation of pneumococcal vaccine in patients with Hodgkin's disease is complicated by frequent splenectomy [4]; however, one study showed that untreated patients with that disease responded to pneumococcal vaccine similarly to normal controls [7]. Among patients with multiple myeloma, antibody responses were impaired [8], but less so among those patients not receiving chemotherapy (Schmid *et al.*, *Clin Res* 1979, **27**, 355A).

Few studies have been performed in patients with solid tumors; in patients with head and neck cancer who received pneumococcal vaccination while they were receiving radiotherapy — a situation close to that in this study — there was no significant antibody response [9].

In our study, most patients received radiotherapy or chemotherapy soon after the injection of the vaccine (median duration between vaccination or placebo administration and therapy: 6 days, range: 0–38); although we found a modest but significant increase of the pneumococcal antibodies against 11 our of 17 serotypes among the patients who were vaccinated, it is possible that antineoplastic therapy might have impaired the formation of anti-

Table 4. Levels of antipneumococcal antibodies against 16 antigens in patients receiving placebo (PL)

Patients	Anti-cancer therapy		Time elapsed (days) between placebo and therapy	Antigens							
	Before PL	After PL		1	2	3	4	6A	7F	8	9N
1. DEZ...*	None	RXT	11	(1) 6.85	0.90	347	24943	2461	452	227	11.8
				(2) 1.33	1.43	1.15	2.28	2.55	1.17	1.55	1.21
2. CAU...	RXT	CT (CDDP + VP16)	13	7.11	9.99	313	12435	1705	444	199	11.5
				0.90	0.95	1.05	4.42	0.17	1.8	1.2	2.74
3. ALV...	RXT	CT (CDDP + VP16)	13	9.98	2.07	469	4147	1264	974	275	39.5
				1.01	0.84	0.81	9.45	4.57	0.94	1.06	1.9
4. DEL...	RXT	RXT	21	4.99	0.81	333	18741	1523	791	170	20.2
				0.95	1.01	1.03	1.87	5.93	1.03	0.99	0.74
5. LEO...	CT (CDDP + VP16)	RXT	0	4.68	0.75	293	50034	2716	718	238	26.4
				1.23	1.10	1.07	1.32	0.94	0.92	0.87	0.83
6. SOL...	none	CT (CDDP + VP16)	0	6.29	0.96	347	28362	5265	929	253	323
				0.89	1.05	1.07	0.33	2.29	1.06	0.97	0.62
7. MOR...	none	CT (CDDP + VP16)	6	4.07	1.06	310	20109	2333	369	220	15.6
				0.99	0.87	1.10	0.84	1.78	0.98	1.09	1.13
8. DEM...	none	none	—	16.25	2.55	929	98306	19304	4434	1359	38.1
				1.20	0.72	1.2	1.24	0.3	0.76	0.9	2.87
9. CAL...	RXT	none	—	3.58	0.60	215	7563	503	366	123	13.1
				0.96	1	1.01	1.07	0.95	1.04	1	1.07
10. AJE...	RXT surgery	CT (CDDP + VP16)	4	4.25	0.71	237	13232	20.84	473	143	19.4
				1.10	1.01	0.86	1.12	0.67	0.95	0.88	0.73
11. VAN...	none	RXT	0	3.04	0.48	190	4341	299	330	87	8.4
				0.75	1.02	1.01	0.85	0.8	0.99	1	1.1
12. MAE...*	none	RXT	0	10.76	1.83	623	205535	18653	2142	679	21.4
				0.83	0.98	0.81	0.77	0.67	0.86	0.82	3.49

Patients	Anti-cancer therapy		Time elapsed (days) between placebo and therapy	Antigens							
	Before PL	After PL		11A	12F	14	17F	18C	19F	23F	25
1. DEZ...*	None	RXT	11	284†	1205	5164	5376	452	986	7467	10.8
				0.9‡	1.26	0.9	0.79	0.94	0.74	0.47	0.96
2. CAU...	RXT	CT (CDDP + VP16)	13	139	1627	6446	12104	380	578	5017	11.6
				1.13	0.86	1.17	0.78	2.38	1.29	0.69	1.45
3. ALV...	RXT	CT (CDDP + VP16)	13	624	2363	10512	10500	1400	1712	5052	39.4
				1.57	0.59	1.3	1.26	0.91	1.26	1.7	0.98
4. DEL...	RXT	RXT	21	123	694	3834	5160	416	474	4389	10.8
				1.61	1.05	0.95	0.71	0.95	1	0.69	0.98
5. LEO...	CT (CDDP + VP16)	RXT	0	60815	1367	5010	5502	410	496	1947	10
				1.17	1.33	0.85	1.27	0.89	0.83	0.86	1.02
6. SOL...	none	CT (CDDP + VP16)	0	233	1283	3994	16084	374	636	2148	11.8
				0.99	1.02	0.99	0.86	1.06	0.89	0.84	0.96
7. MOR...	none	CT (CDDP + VP16)	6	248	1449	3364	3608	290	366	1413	8.2
				2.14	0.98	1.12	1.13	0.99	1.2	0.87	1.1
8. DEM...	none	none	—	4871	12035	21832	25438	2134	1498	8327	59
				3.85	0.77	0.93	3.28	1.27	0.91	0.79	0.76
9. CAL...	RXT	none	—	168	248	4200	4316	304	346	643	8.6
				1.03	0.84	0.81	0.91	1.05	1.11	0.95	1.07
10. AJE...	RXT surgery	CT (CDDP + VP16)	4	455	278	14224	5328	662	426	796	10.2
				1.69	0.92	0.68	0.97	0.76	0.79	0.91	0.82
11. VAN...	none	RXT	0	671	98	2550	2754	414	292	497	6.8
				1.14	1.02	1.03	1.0	1.04	1.16	0.91	1.21
12. MAE...*	none	RXT	0	853	3145	12860	44704	1188	948	3479	30.8
				1.24	1:21	0.95	0.87	0.93	0.83	1.01	0.69

* Developed pneumococcal infection; † Initial antibody level. ‡ Multiple of initial level after placebo.

Table 5. Levels of antipneumococcal antibodies against 16 antigens in patients receiving vaccination (VA)

Patients	Anti-cancer therapy Before VA	After VA	Time elapsed (days) between placebo and therapy	Antigens 1	2	3	4	6A	7F	8	9N
13. BOU...	none	CT liposomes	32	14.82†	1.26	388	40169	13364	840	122	9
		C8-240		0.86‡	2.62	0.76	1.56	0.73	0.81	0.93	1.91
14. HEN...	none	RXT	0	3.57	0.61	208	5209	512	316	108	6.5
				2.21	2.75	1.45	2.52	4.62	3.66	1.79	2.43
15. PEE...	none	RXT	0	15.52	2.10	745	42923	1826	849	471	29.6
				1.08	4.03	1.07	1.36	0.8	1.6	1.45	0.83
16. FEY...	none	CT (AVE)	17	11.84	2.60	526	157659	508	615	1225	19.6
				4.14	1.48	1.01	0.63	34.46	3.58	0.91	6.82
17. COL...	none	CT (CAVE)	8	8.58	1.57	407	99949	4940	1278	288	44.3
				1.18	1.31	1	1.73	1.83	3.49	1.5	4.4
18. VAN...	none	CT (CDDP	27	15.17	1.86	697	56422	25155	3800	858	64.6
		+ VP16)		3.66	2.27	1.12	1.68	1.32	16.12	12.88	39.06
19. BAL...	none	RXT	0	4.17	0.82	266	6515	39526	671	169	24.1
				5.39	9.98	1.07	3.22	0.41	4.24	7.23	79.64
20. MOR...	RXT	CT (CDDP	0	11.09	1.75	550	48403	20982	1781	419	20.6
		+ VP16)		1.10	2.59	1.14	2.01	1.68	6.54	2.83	18.67
21. GER...	RXT	CT (CDDP	14	5.57	1.03	343	70278	5667	990	194	17.2
		+ VP16)		5.0	1.29	0.95	2.57	1.75	1.36	1.68	1.66
22. ROS...	none	RXT	9	3.65	0.69	255	10756	1583	466	104	19.4
				1.42	1.48	1.05	1.95	1.4	2.32	3.07	0.55
23. MEN...	RXT	CT (CDDP	38	15.47	1.78	550	185310	16501	2222	559	65.2
		+ VP16)		1.29	2.25	1.81	0.85	1.1	0.8	1.8	11.43
24. VAN...	none	RXT	0	14.25	1.56	934	112710	19116	752	700	55
				2.38	3.57	0.83	2.71	2.79	1.52	10.46	56.35
25. FRA...	none	CT (CAVE)	17	7.77	1.69	369	22489	5087	564	211	43.4
				4.57	5.78	0.83	4.18	5.02	1.74	2.35	67.51
26.WAC...	none	RXT	0	5.50	0.79	274	13735	3981	367	159	11.7
				0.97	0.97	0.95	0.88	0.47	2.74	0.97	1.15
27. VAN...*	none	CT (CAVE)	8	9.85	1.24	407	19860	16420	455	263	20.4
				0.74	0.85	0.92	0.83	0.2	0.91	0.95	0.85
28. CLE...	none	RXT	5	6.57	0.79	318	20109	3488	540	219	14.4
				1.19	1.35	1.14	1.26	2.6	1.83	1.62	4.9
29. TOS...	none	CT (CAVE)	5	11.20	1.91	539	41523	37420	1004	736	58.2
				1.16	0.88	1.14	1.36	0.57	0.88	1.02	1.3

Patients	Anti-cancer therapy Before VA	After VA	Time elapsed (days) between placebo and therapy	Antigens 11A	12F	14	17F	18C	19F	23F	25
13. BOU...	none	liposomes	32	604.3†	3238	8212	22892	966	512	11633	15.8
				1‡	0.85	12.94	0.99	1.03	1.2	1.26	1.01
14. HEN...	none	RXT	0	74	217	3314	4730	356	300	1109	8.6
				2.91	2.43	3.6	1.94	1.51	5.87	8.95	1.55
15. PEE...	none	RXT	0	637	5080	12990	4664	598	1006	23267	28
				1.54	1.07	2.88	1.74	5.61	1.13	0.72	3.24
16. FEY...	none	CT (AVE)	17	594	2433	10460	3046	534	686	9859	11.8
				8.67	2.26	24.8	3.32	52.43	107.87	3.43	11.46
17. COL...	none	CT (CAVE)	8	3994	2896	8724	5476	2334	792	2788	26.2
				9.48	0.73	0.95	8.74	2.48	1.0	1.46	0.71
18. VAN...	none	CT (CDDP	27	81748	5.847	10406	70380	3740	792	4999	19.8
		+ VP16)		0.01	2.54	7.66	7.41	9.66	32.84	7.17	6.25
19. BAL...	surgery	RXT	0	113	910	7202	7940	552	568	1037	13.4
				25.58	4.34	41.68	7.05	1.04	14.35	21.5	3.16
20. MOR...	RXT	CT (CDDP	0	658	2504	12990	30140	1008	846	2052	21.2
		+ VP16)		2.32	3.21	3.47	3.19	7.67	3.79	15.39	1.11
21. GER...	RXT	CT (CDDP	14	142	1315	5350	9940	456	380	1827	13.6
		+ Vp16)		1.71	1.87	3.49	3.56	10.07	0.52	4.06	1.55
22. ROS...	none	RXT	9	100	229	3026	4140	460	292	793	9.2
				65	1.89	2.03	2.09	0.83	2.29	1.37	4.53

cont'd on p.812.

Table 5 continued

Patients	Anti-cancer therapy		Time elapsed (days) between placebo and therapy	Antigens							
	Before VA	After VA		11A	12F	14	17F	18C	19F	23F	25
23. MEN...	RXT	CT (CDDP + VP16)	38	1300	5359	15892	32582	2170	922	5052	24.4
				2.16	1.34	39.83	1.76	241.19	2.38	3.32	4.1
24. VAN...	none	RXT	0	917	6861	272.54	39682	1948	872	8717	30.2
				4.92	1.09	0.99	5.4	917.76	9.0	4.06	3.09
25. FRA...	none	CT (CAVE)	17	1019	2093	16054	13762	1680	762	2797	21.6
				6.8	11.27	1.82	4.37	25.37	58.67	27.97	11.3
26.WAC...	NONE	RXT	0	4915	453	3798	3956	538	792	1560	10.2
				1.15	0.94	1.2	1.38	1.11	0.8	1.65	1.05
27. VAN...*	none	CT (CAVE)	8	1981	2063	6098	7868	590	516	2321	28.8
				0.39	0.92	0.81	0.78	0.86	0.72	0.8	0.5
28. CLE...	none	RXT	5	177	1110	5770	6580	640	516	1101	12.6
				2.39	0.88	7.18	2.19	16.25	1.08	4.07	8.1
29. TOS...	none	CT (CAVE)	5	711	593	21182	70380	398	986	4895	31
				1.11	0.99	0.93	2.94	8.87	0.87	0.7	1.07

* Developed pneumococcal infection. † Initial antibody level. ‡ Multiple of initial antibody level after vaccination.

Table 6. Mean increase of antibody levels after vaccination

Pneumococcal types	Mean
1	2.2
2	2.6
3	1.0
4	1.8
6A	3.6
7F	3.1
8	3.1
9N	17.6
11A	4.6
12F	2.2
14	9.1
17F	3.4
18C	76.6
19F	14.3
23F	6.3
25	3.7

bodies against some pneumococcal antigens, making the potential benefit of vaccination undemonstrable. An alternative explanation might be the intrinsic defect in immune competence in patients with bronchogenic carcinoma [10].

It may be speculated that for patients with bronchogenic carcinoma and in whom vaccination against pneumococcal infection (and other diseases) is desired, radiotherapy and/or chemotherapy should be sufficiently delayed to allow an adequate antibody response. Such a conclusion has been reached in studies with other types of cancer [4]; however, delays in instituting therapy in cancer patients is often difficult for clinical and psychological reasons. The potential benefit or adverse effects of such an attitude should be evaluated in properly controlled studies in which therapy would be delayed by 3 or 4 weeks after immunization.

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