

**A Commentary Regarding Methods of Determining Rare
Adverse Reactions to Vaccines as Exemplified by
Experiences with Hepatitis B Vaccine**

Burton A. Waisbren, M.D., F.A.C.P.*, F.I.D.S.A.†

Waisbren Clinic

2315 N. Lake Drive

Suite 815

Milwaukee, WI 53211

* Fellow American College of Physicians

† Fellow Infectious Disease Society of America

INTRODUCTION

Immunization Safety Reviews by the prestigious Institute of Medicine have emphasized the epidemiologic methods cannot establish, without absolute certainty, that a vaccine will never cause an adverse event.¹ This does not mean that these methods should not be explored for possible useful information.

In this commentary, six methods of determining whether rare adverse events occur after vaccination are presented and critiqued. Their use in the study of possible adverse events caused by the hepatitis B vaccine is used as an example. Each has some value and taken as a whole, they might yield information regarding the incidence of untoward events and the mechanism by which they might occur.

The six methods are: preclinical testing,² post marketing surveillance,³ the Vaccine Adverse Events Reporting System (VAERS),⁴ the Vaccine Safety Datalink (VSD) Project,⁵ case control studies,⁶ and case reports in the peer reviewed medical literature.⁷ Reference is made to new approaches to the analysis of VAERS data.⁸ Particular emphasis is placed on the necessity for large databases for use in studies that are done to reveal increased risk of rare adverse events by case control methods.^{9,10,11,12} The importance of individual case reports is also emphasized.

REVIEW OF EACH METHOD

1. Pre-licensure Studies: Because small numbers of patients are given a vaccine prior to its release, rare complications may not be seen. In the case of yeast derived HBV vaccine a total of only 12,699 subjects were studied with a total of 36,965 doses of the vaccine administered.²

2. Post-marketing Surveillance: A post-marketing surveillance study of HBV vaccination was done three years after its release.³ In this HBV vaccine post-marketing surveillance study, it was estimated that 850,000 individuals received the vaccine between June 1, 1982, and May 31, 1985. The study found, "During that period, a total of 41 reports were received for one of the following neurologic adverse events: convulsions (five cases), Bell's palsy (10 cases), Guillain-Barré syndrome (nine cases), lumbar radiculopathy (five cases), brachial plexus neuropathy (three cases), optic neuritis (five cases), and transverse myelitis (four cases)." The incidence of the diseases reported after HBV vaccine was compared with the reported incidence of these diseases in normal populations. It was found that the Guillain-Barré syndrome occurred in significantly higher number of individuals who had received the vaccine than there would have been expected in normal populations. The conclusion of the authors was that this finding should not deter patients who had definite risk factors regarding the HBV from taking the vaccine. No mention was made as to whether individuals who have few risk factors should or should not be vaccinated. It is of interest that this post marketing surveillance study did unearth a number of adverse events that took years to reach the medical literature via case reports. Could it be that these adverse events surfaced because they were actively searched for whereas the VAERS, to be discussed next, is a passive surveillance system?

3. Vaccine Adverse Events Reporting System (VAERS): VAERS was established in 1990 as a cooperative venture between the Federal Food and Drug Administration (FDA) and the Center for Disease Control and Prevention (CDC).⁴ It is a passive surveillance system that solicits reports of all possible adverse events that could have occurred from a vaccination. From the VAERS beginning, Dr. Robert Chen, the Chief of the Vaccine Safety and Development Activity, National Immunization Program (NIP), CDC, has presented six caveats regarding interpretation of the data included in VAERS. They are, "Dose distribution data not readily available to calculate rates, under-reporting, biased reporting/lack of representativeness, inadequate information provided by reporter, confounding by drug and disease, and no comparison group, limiting causality assessment."⁴ In spite of these caveats, recent study of the VAERS data, suggests that VAERS can be valuable in identifying adverse events that follow specific vaccines.

In June 2001, Geier and Geier reported in the *Annals of Internal Medicine*, a potential use of the VAERS data.¹³ Using the data made available through VAERS, they analyzed four types of immunologic reactions associated with vaccines that had been reported between 1990 and 1997. Their analysis indicated, "That HBV vaccine not only is associated with large numbers of potentially serious reactions but seems to be associated with the most reactions of any vaccine, especially reactions related to immune complications."¹³ The CDC did not make available to the Geiers, the number of HBV vaccine shots given annually nor the ages of the recipients.

Now the entire VAERS database is available on the internet. It includes all reports of adverse events received by VAERS between 1990 and May 31, 2004.¹⁴ In addition, the total net vaccine doses distributed between 1991 and 2001 has been published by the CDC.¹⁵ Thus, data is available for both adverse events reported and estimates of number of vaccines given based on net vaccine doses distributed for 1991-2001.

With this additional information available, the Geiers further analyzed the VAERS database. They examined the adverse reactions reported to follow HBV vaccine. As a control, they also examined adverse events reported to follow adult tetanus-diphtheria (Td) vaccine. Their conclusion was, "Our study demonstrates that adult HBV (vaccine) is statistically associated not

only with acute neuropathy, neuritis, myelitis, vasculitis, thrombocytopenia, gastrointestinal disease, multiple sclerosis, and arthritis, but some of these patients go on to develop chronic adverse reactions that persist for a least 1 year following HBV (vaccine).⁸

Following the Geier's lead, and using the data available on the internet from VAERS and the CDC, we studied six adverse events reported to follow HBV, influenza, and MMR vaccines that were received by VAERS from 1991-2001.^{14,15} Table 1 shows the number of adverse events broken down by vaccine, adverse event, and age. Figure 1 compares the reported adverse events to total net vaccine doses distributed.

Although the percentages are admittedly low, one can see that the pattern of adverse events reported for each vaccine vary greatly. By gross pattern recognition, this data seems to indicate that it might be worthwhile to investigate mechanisms that might cause an inordinate number of adverse events to occur due to a certain vaccine.

The VAERS website states, "The purpose of VAERS is to detect possible signals of adverse events associated with vaccines. Additional scientific investigations are almost always required to properly validate signals from VAERS and establish a cause and effect relationship between a vaccine and an adverse event."¹⁶ In this frame of reference, studies of demyelinating diseases that were found to occur after hepatitis B vaccine has yielded suggestions that this complications occurs in individuals with certain human lymphocyte antigens (HLA) patterns.^{17,18} In addition, a study of a single person who developed MS after HBV vaccination revealed that anti-myelin T-cells appeared to have been evoked after this vaccination.¹⁹

Vaccine Safety Datalink (VSD) Project: The VSD project began in 1990 with the express purpose of rigorously evaluating concerns about vaccine safety.⁵ The plan was to use for evaluation, the HMO records of 6 million people in the United States who were members of managed care programs. How many of those 6 million individuals would need to be included in a study database to draw valid conclusions regarding a rare adverse event is a valid question?

When the statistical method of Frank, et al is used to determine the number of individuals needed in a database to establish increased rates of reactions to a vaccine, one finds that millions of individuals would be needed to statistically establish a rare reaction.^{9,10} (Table 2)

A power analysis using the method of Dupont showed that in order to detect a 10% increase in the incidence of multiple sclerosis due to vaccination with 90% power, over 10,000 cases of multiple sclerosis would be needed.¹¹

Using the statistical program Stata, version 7 (Stata Corporation, College Station, TX) to calculate sample size, one would conclude that a pool of 3.4 million subjects would be needed to show that the prevalence of multiple sclerosis after hepatitis B vaccination increases from 2 per 100,000 to 4 per 100,000.¹² (Table 3)

These statistical methods illustrate the need for huge databases to demonstrate the occurrence of rare adverse events after vaccination. They also shed doubt on conclusions reached from studies done with smaller databases.

A study which appeared in the Archives of Neurology, illustrates the limitations of the VSD project.²⁰ This study included 440 cases of demyelinating diseases. Three hundred thirty-two patients had MS and 108 had optic neuritis (OP). Nine hundred and fifty controls were included. The conclusion of this article stated, "Vaccination against hepatitis B, influenza, tetanus, measles, or rubella is not associated with an increased risk of multiple sclerosis or optic neuritis".²⁰ Not mentioned in the study was the incidence rate of MS and OP or the number of individuals included in the database from which the conclusions were drawn. Unless millions of the individuals available to the VSD project were used, it is doubtful that the conclusion

regarding the relative risk was based on statistics of enough power to reach this determination.^{9,10,11,12} The correct conclusion probably should have been that the study did not demonstrate an association between the vaccines and the development of MS or OP.

All of the above in no way denigrates the use of the VSD Project to study possible adverse effects of vaccines as long as the strength of the statistics used is great enough to reveal an increase in relative risk of the adverse effect being studied.^{9,10,11,12}

Case Control Studies: This method pairs subjects that received an intervention with those who did not.⁶ The purpose is to determine whether or not a particular intervention increases the relative risk of the occurrence of a complication. A problem with this method is that a very large number of subjects have to be compared to demonstrate a rare adverse event. (Table 2 and 3)^{9,10,11,12}

An article that appeared in the New England Journal of Medicine (NEJM) in February 2001 illustrates this problem.²¹ This article used as its database, the Nurses' Health Study and Nurses' Health Study II. There were 238,371 nurses in this database. The analyses included 192 women with multiple sclerosis and 645 matched controls. The conclusion of this article was, "These results indicate no association between hepatitis B vaccination and the development of multiple sclerosis."²¹ A more accurate conclusion would be that the study did not demonstrate an association between HBV vaccine and the developments of MS.

A conclusion that the study was based on an underpowered statistical analysis is reasonable when you take into account the number of subjects needed to prove and increased relative risk as illustrated by Table 2 and 3.^{9,10,11,12}

Of note is that this study was supported by grants from the National Institutes of Health (NIH) and a research laboratory that is a division of one of the HBV vaccine manufactures.²¹ Some of the statisticians who were listed as authors of the article were affiliated with that same research laboratory. While the affiliations of these statisticians are listed, no mention was made of the possible conflicts of interest involved with them being employed by or with the study being partially supported by grants from a division of a HBV vaccine manufacturer. In cases such as this, some journals choose to include information about the sponsor's involvement in the methods section of the article.²²

5. Case Reports: Lasagna, the famed pharmacologist of John Hopkins University Medical School wrote in 1984, "Spontaneous reporting by the alert and competent doctor will, in the foreseeable future, remain the most important source of new leads about drugs."⁷

More recently, Johnson in his book *Emergence* stated, "the Web itself-the largest and most advanced man-made self organizing system on the planet-is only now becoming capable of true collective intelligence."²³

Following the suggestions of Lasagna and Johnson, we did a literature search using the criteria of "hepatitis b vaccine and publication type of case reports" to find observations about untoward results that the authors felt might be caused by HBV vaccination. We found 198 articles, by 733 authors, in 111 peer reviewed journals from 21 different countries. Ten of these articles are referenced.^{17,18,24-31} (The complete bibliography of the 198 articles is available upon request from the author.) The vast majority of these articles reported autoimmune diseases that followed hepatitis B vaccination. There were 36 reports of Central Nervous System (CNS) and Peripheral Nervous System (PNS) disease, 16 of vasculitis, 16 of Lichenoid reactions, 13 of arthritis, 13 of autoimmune hematologic disease, and 8 of lupus.

I know of no other vaccine that has engendered as many articles about acquired autoimmune diseases that have followed any vaccination. When one considers that the Web is a

communications device used by literally thousands of physicians around the world it might be fair to postulate that these articles represent a database that has revealed a significant group of complications. This of course is what was postulated by Lasagna and Johnson.^{7,23}

These reports have the advantage of credibility over those of VAERS because they are all made by *bona fide* physicians and academic scientists whereas, VAERS accepts reports regardless of the training of those who submit them.⁴

DISCUSSION

Frank and his co-authors have likened searching for a rare adverse reaction that may follow vaccination to searching for “needles in a haystack”.¹⁰ Each of the six methods discussed has the possibility of acting as a magnet to pull from the haystack, the needle that suggests an adverse event occurs.

Pre-clinical testing may reveal common serious problems, particularly of intolerance to the vaccine.²

The post-marketing surveillance study done on hepatitis B vaccine produced some hints that acquired autoimmune syndromes might follow hepatitis B vaccination.³ The most convincing finding of this study was the increase in the incidence of Guillain-Barré syndrome when it was compared to the incidence in the general population who had not received the vaccination.³

Findings presented in the commentary suggest that in spite of the caveats published regarding VAERS, that the vast amount of data that it has accrued might be harvested to show distinctive patterns of adverse events that might signal further study is needed. (Figure 1)

The VSD project might well reveal valuable information about adverse events provided that enough of the six million subjects it has available are studied. These adverse events would need to have a great enough incidence to be revealed by the size of the databases. (Table 2 and 3)

Similarly, case control studies can do the same as long as they also use databases large enough to reveal adverse events by the statistical analysis used.

Case reports, which have been used in medical teaching since *time immemorial*, are a mechanism by which physicians can alert colleagues worldwide about their observations.

How might the information presented in this commentary be of help to physicians who note an unusual reaction to a vaccine? In addition to sharing this experience with their local colleagues, they can use the VAERS database to see how many similar reactions have been reported.¹⁴ They can review epidemiological studies that may have been done regarding the adverse event that they observed. In doing this, they should examine who has published these studies, the power of the statistical analysis used, and whether there might be the appearance of conflicts of interest among the authors and the sponsors of the study. They can use sites available on the Web such as *Pubmed* to look for articles describing similar adverse reactions. They might submit a case report to a peer reviewed journal regarding their observation. In the aggregate, case studies of this type might help reveal patterns of adverse results that when added to those that are reported to VAERS will lead to studies of mechanisms. When a patient asks about possible adverse results from vaccines, the fact should be shared with them that there is no way to absolutely guarantee that a vaccination will never cause an adverse result.¹ In no way should vaccinations that have long since proven their value be arbitrarily rejected. On the other hand these vaccinations should be subjected to ongoing scrutiny in regard to untoward reactions that they may cause.

Finally, risk/benefit ratios must be considered when any new vaccination program is considered. Certainly people with high risk of exposure to the communicable disease should be vaccinated. However, caution must be exercised in adopting programs in which vaccine recipients have little chance of being exposed to the disease for which the vaccine affords protection.

SUMMARY AND CONCLUSION

Six methods of searching for significant adverse events that occur after vaccination are discussed. All have some potential to be of use as long as statistical methods used to determine if a problem exists have enough power to reveal that an adverse event has occurred. It must be remembered that, "absence of proof is not proof of absence".

ACKNOWLEDGEMENTS

I would like to acknowledge the help of statisticians Rollin Brant, PhD. of University of Calgary, William Dupont, PhD. of Vanderbilt University, Susan Waisbren, PhD. of Harvard University and Elizabeth Allred, MS of Boston Children's Hospital who were kind enough to review the statistics in this paper and the efforts of Sharon Wochos, MLA of Columbia St. Mary's Hospitals and Kathleen Jury, BA of the Waisbren Clinic, who helped in the collection of data.

TABLE 1

Vaccine	Hepatitis B	Influenza	MMR
Net doses distributed	276,503,724	528,736,717	145,581,091
Reports of adverse events	30,287	15,236	22,870
by age <1	6,561	38	170
1-6	3,034	352	16,072
7-17	4,352	395	2,612
18-64	12,305	9,060	3,055
<u>> 65</u>	202	3,440	10
Unknown	3,833	1,951	951
Alopecia	176	12	20
by age <1	10	0	0
1-6	18	0	11
7-17	50	1	3
18-64	81	8	5
<u>> 65</u>	2	3	0
Unknown	15	0	1
Autism	47	0	187
by age <1	19	0	4
1-6	24	0	159
7-17	3	0	3
18-64	0	0	1
<u>> 65</u>	0	0	0
Unknown	1	0	20
Encephalitis	50	44	80
by age <1	13	0	1
1-6	4	1	59
7-17	10	2	9
18-64	20	22	8
<u>> 65</u>	0	14	0
Unknown	3	5	3
Facial paralysis	182	187	46
by age <1	3	0	0
1-6	13	0	18
7-17	42	5	15
18-64	98	122	13
<u>> 65</u>	1	44	0
Unknown	25	16	0
Guillain-Barré	84	512	47
by age <1	2	0	0
1-6	7	4	19
7-17	10	8	14
18-64	51	316	13
<u>> 65</u>	1	148	0
Unknown	13	36	1
Multiple sclerosis	101	20	4
by age <1	0	0	0
1-6	0	0	0
7-17	10	0	0
18-64	76	16	4
<u>> 65</u>	0	2	0
Unknown	15	2	0

FIGURE 1

**Comparison of Adverse Events Received by VAERS to the
Total Net Vaccine Doses Distributed
1991-2001**

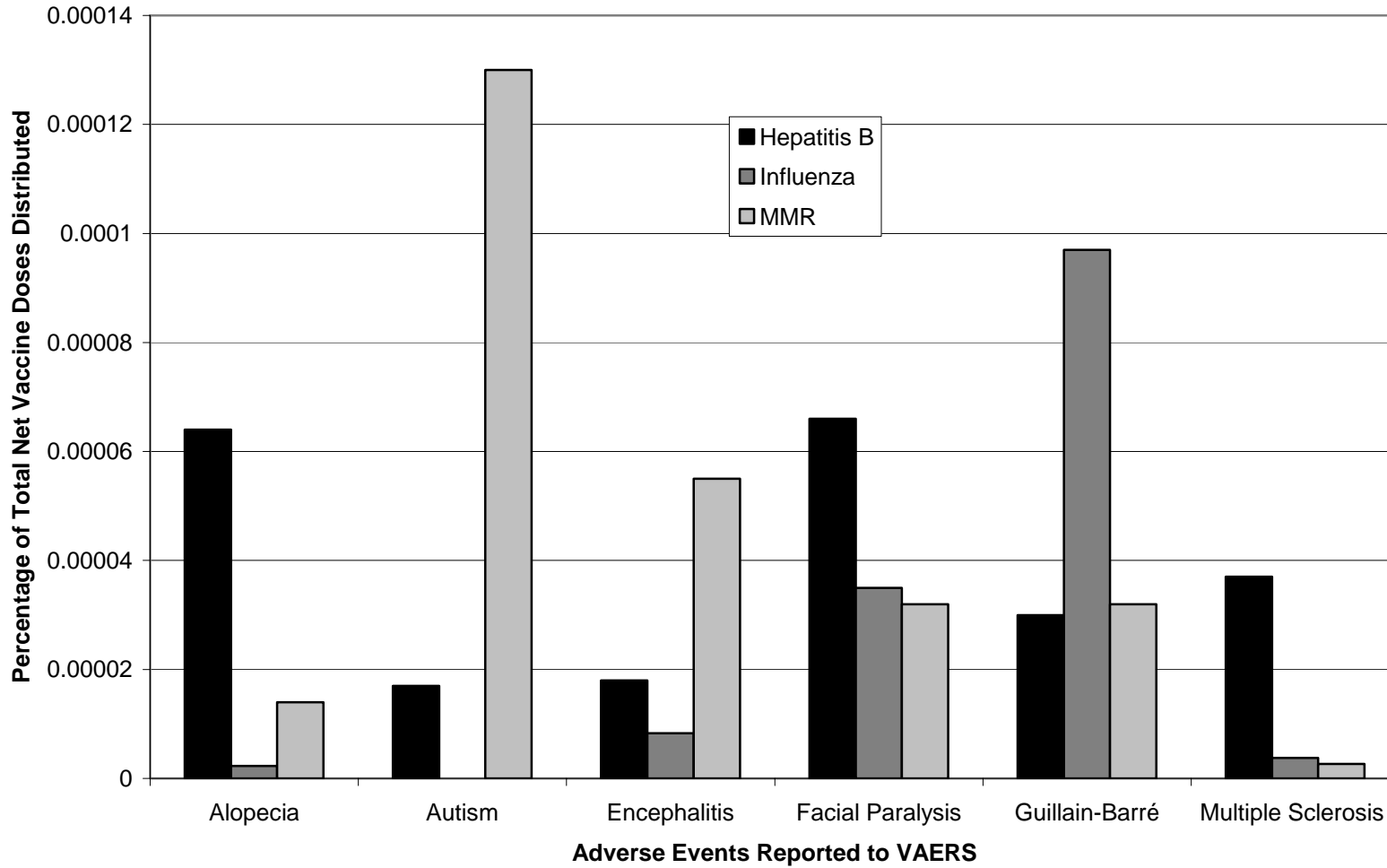


TABLE 2

Number of individuals needed in a database to establish increased rates of reactions to a drug with a p-value of .05. (alpha=.05 one sided)*†

Incidence of reaction	rr = 1.3	rr = 1.5	rr = 2.0
2 per 100,000	3768337	1431760	401875
4 per 100,000	1884127	715863	200932
8 per 100,000	942022	357915	100460
12 per 100,000	627987	238599	66970
25 per 100,000	301390	114510	32140
50 per 100,000	150654	57238	16065
100 per 100,000	75285	28602	8027

* <http://www.health.ucalgary.ca/~rollin/stats/ssize/b2.html>

† Based on Frank JW, Coates RA, Brant R, Garbutt JM. Sample sizes for needles in a haystack: the case of HIV seroprevalence surveys. Can J Public Health. 1990 Jan-Feb;81(1):50-2.

TABLE 3

Calculation used to determine that a sample size of about 3.4 million would be needed to show that the prevalence of multiple sclerosis after hepatitis B vaccination increases from 2 per 100,000 to 4 per 100,000*

Calculate sample size with varying values of alpha and power.[†]

Alpha (type I error)	Power [Beta (type II error) = 1 – power]		
	.90	.80	.70
.05	1,674,572 [‡]	1,275,336	1,023,339
.10	1,382,729	1,024,916	802,714

* Assumptions:

The prevalence of multiple sclerosis in unvaccinated subjects is 2 per 100,000 (.00002).

The prevalence of multiple sclerosis in vaccinated subjects is 4 per 100,000 (.00004).

There are an equal number of vaccinated and unvaccinated subjects.

[†] Calculations kindly provided by Elizabeth Allred of the Neuroepidemiology Unit, Boston Children's Hospital using Stata, version7 (Stata Corporation, College Station, TX).

[‡] You would need 1,674,572 subjects in each group or a total sample of about 3,400,000 to show a significant increase in the rate of multiple sclerosis when alpha = .05 and power is .90.

REFERENCES

1. Stratton K, Gable A, Shetty, P, McCormick M, editors. Immunization Safety Review Committee, Board on Health Promotion and Disease Prevention. Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism. Washington, DC: National Academies Press; 2001. p. 45.
2. Andre FE. Summary of safety and efficacy data on a yeast-derived hepatitis B vaccine. *Am J Med.* 1989 Sep 4;87(3A):14S-20S.
3. Shaw FE Jr, Graham DJ, Guess HA, Milstien JB, Johnson JM, Schatz GC, et al. Postmarketing surveillance for neurologic adverse events reported after hepatitis B vaccination. Experience of the first three years. *Am J Epidemiol.* 1988 Feb;127(2):337-52.
4. Chen RT, Rastogi SC, Mullen JR, Hayes SW, Cochi SL, Donlon JA, et al. The Vaccine Adverse Event Reporting System (VAERS). *Vaccine.* 1994 May;12(6):542-50.
5. Chen RT, Glasser JW, Rhodes PH, Davis RL, Barlow WE, Thompson RS, et al. Vaccine Safety Datalink project: a new tool for improving vaccine safety monitoring in the United States. The Vaccine Safety Datalink Team. *Pediatrics.* 1997 Jun;99(6):765-73.
6. Riegelman RK, Hirsch RP. Studying a study and testing a test: How to read the medical literature. Boston: Little, Brown and Company;1989. p.9.
7. Lasagna L. Techniques for ADR reporting. In: Bostrom, H and Ljungstedt, N, editors. Detection and Prevention of adverse drug reactions Sixteenth Skandia International Symposia. Stockholm: Almqvist and Wiksell International; 1984. pp. 146-51.
8. Geier DA, Geier MR. Chronic adverse reactions associated with hepatitis B vaccination. *Ann Pharmacother.* 2002 Dec;36(12):1970-1. No abstract available.
9. Frank JW, Coates RA, Brant R, Garbutt JM. Sample sizes for needles in a haystack: the case of HIV seroprevalence surveys. *Can J Public Health.* 1990 Jan-Feb;81(1):50-2.
10. University of Calgary [homepage of the internet]. Calgary: University of Calgary; c2003 [cited 2004 Aug 15] Inference for Proportions: Comparing Two independent Samples; Available from: <http://www.health.ucalgary.ca/~rollin/stats/ssize/b2.html>.
11. Dupont WD. Power calculations for matched case-control studies. *Biometrics.* 1988 Dec;44(4):1157-68.
12. StataCorp. Stata Statistical Software: Release 7.0. College Station, Texas, US: Stata Corporation (2001).

13. Geier MR, Geier DA. Immunologic reactions and hepatitis B vaccine. *Ann Intern Med.* 2001 Jun 19;134(12):1155.
14. VAERS: Vaccine Adverse Events Reporting System [homepage on the internet]. Rockville (MD): VAERS; [Updated 2004 Aug 11; cited 2004 Aug 15]. VAERS Public Data Download Instructions; Available from: <http://www.vaers.org/data.htm>.
15. Zhou W, Pool V, Iskander JK, English-Bullard R, Ball R, Wise RP, et al. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VAERS)-- United States, 1991-2001. *MMWR Surveill Summ.* 2003 Jan 24;52(1):1-24. Erratum in: *MMWR Morb Mortal Wkly Rep.* 2003 Feb 14;52(06):113.
16. VAERS: Vaccine Adverse Events Reporting System [homepage on the internet]. Rockville (MD): VAERS; [cited 2004 Aug 15]. VAERS Data: Guide To Interpreting Case Report Information Obtained From The Vaccine Adverse Event Reporting System (VAERS); Available from: <http://www.vaers.org/info.htm>.
17. Herroelen L, de Keyser J, Ebinger G. Central-nervous-system demyelination after immunisation with recombinant hepatitis B vaccine. *Lancet.* 1991 Nov 9;338(8776):1174-5.
18. Kaplanski G, Retornaz F, Durand J, Soubeyrand J. Central nervous system demyelination after vaccination against hepatitis B and HLA haplotype. *J Neurol Neurosurg Psychiatry.* 1995 Jun;58(6):758-9.
19. Gran B, Bielekova B, McFarland HF, Martin R. Development of multiple sclerosis after hepatitis B vaccination: an immunologic case report. *Neurology.* 2000;54 Suppl 3:A164.
20. DeStefano F, Verstraeten T, Jackson LA, Okoro CA, Benson P, Black SB, et al. Vaccinations and risk of central nervous system demyelinating diseases in adults. *Arch Neurol.* 2003 Apr;60(4):504-9.
21. Ascherio A, Zhang SM, Hernan MA, Olek MJ, Coplan PM, Brodovicz K, et al. Hepatitis B vaccination and the risk of multiple sclerosis. *N Engl J Med.* 2001 Feb 1;344(5):327-32.
22. [icmje.org](http://www.icmje.org) [homepage on the internet]. Philadelphia (PA): International Committee of Medical Journal Editors [Updated 2003 Nov; cited 2004 Aug 15]. Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication; Available from: <http://www.icmje.org/>.
23. Johnson S. *Emergence: the connected lives of ants, brains, cities, and software.* New York: Scribner Book Company; 2001. p.226.
24. Nadler JP. Multiple sclerosis and hepatitis B vaccination. *Clin Infect Dis.* 1993 Nov;17(5):928-9.

25. Deisenhammer F, Pohl P, Bosch S, Schmidauer C. Acute cerebellar ataxia after immunisation with recombinant hepatitis B vaccine. *Acta Neurol Scand.* 1994 Jun;89(6):462-3.
26. Zaas A, Scheel P, Venbrux A, Hellmann DB. Large artery vasculitis following recombinant hepatitis B vaccination: 2 cases. *J Rheumatol.* 2001 May;28(5):1116-20.
27. Schupp P, Vente C. Lichen planus following hepatitis B vaccination. *Int J Dermatol.* 1999 Oct;38(10):799-800.
28. Vautier G, Carty JE. Acute sero-positive rheumatoid arthritis occurring after hepatitis vaccination. *Br J Rheumatol.* 1994 Oct;33(10):991.
29. Ronchi F, Cecchi P, Falcioni F, Marsciani A, Minak G, Muratori G, Tazzari PL, Beverini S. Thrombocytopenic purpura as adverse reaction to recombinant hepatitis B vaccine. *Arch Dis Child.* 1998 Mar;78(3):273-4.
30. Tudela P, Marti S, Bonal J. Systemic lupus erythematosus and vaccination against hepatitis B. *Nephron.* 1992;62(2):236
31. De Keyser F, Naeyaert JM, Hindryckx P, Elewaut D, Verplancke P, Peene I, et al. Immune-mediated pathology following hepatitis B vaccination. Two cases of polyarteritis nodosa and one case of pityriasis rosea-like drug eruption. *Clin Exp Rheumatol.* 2000 Jan-Feb;18(1):81-5.