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Comparison of VAERS fetal-loss reports during three consecutive influenza seasons: Was there a synergistic fetal toxicity associated with the two-vaccine 2009/2010 season?

GS Goldman

Abstract

The aim of this study was to compare the number of inactivated-influenza vaccine–related spontaneous abortion and stillbirth (SB) reports in the Vaccine Adverse Event Reporting System (VAERS) database during three consecutive flu seasons beginning 2008/2009 and assess the relative fetal death reports associated with the two-vaccine 2009/2010 season. The VAERS database was searched for reports of fetal demise following administration of the influenza vaccine/vaccines to pregnant women. Utilization of an independent surveillance survey and VAERS, two-source capture–recapture analysis estimated the reporting completeness in the 2009/2010 flu season. Capture–recapture demonstrated that the VAERS database captured about 13.2% of the total 1321 (95% confidence interval (CI): 815–2795) estimated reports, yielding an ascertainment-corrected rate of 590 fetal-loss reports per million pregnant women vaccinated (or 1 per 1695). The unadjusted fetal-loss report rates for the three consecutive influenza seasons beginning 2008/2009 were 6.8 (95% CI: 0.1–13.1), 77.8 (95% CI: 66.3–89.4), and 12.6 (95% CI: 7.2–18.0) cases per million pregnant women vaccinated, respectively. The observed reporting bias was too low to explain the magnitude increase in fetal-demise reporting rates in the VAERS database relative to the reported annual trends. Thus, a synergistic fetal toxicity likely resulted from the administration of both the pandemic (A-H1N1) and seasonal influenza vaccines during the 2009/2010 season.

Keywords

Human toxicology, immunization, influenza vaccine, spontaneous abortion, stillbirth, Thimerosal

Introduction

Since 1997, the Advisory Committee on Immunization Practices (ACIP) has recommended the routine vaccination of pregnant women with trivalent inactivated influenza vaccine (TIV) after the first trimester of pregnancy. This recommendation was expanded in 2004 to include all trimesters of pregnancy.[1]

All previously published studies of pregnant women who were administered with TIV have reported this vaccine as safe during all stages of pregnancy.[2–4] Christian et al. explained the reason for this record of safety: 'The inflammatory response elicited by TIV is substantially milder and more transient than seen in infectious illness.'[5]

Two frequently cited peer-reviewed reports on the safety of influenza vaccination during pregnancy did not reveal any adverse outcomes among 56 women[6] and 180 women.[7] Both these studies, which used 'no Thimerosal' influenza vaccines, had insufficient statistical power to adequately detect and assess complications due to the small sample size. A third follow-up safety study (conducted among 2291

Independent Computer Scientist, Pearblossom, CA, USA

Corresponding author:
Gary S Goldman, Independent Computer Scientist, P.O. Box 847, Pearblossom, CA 93553, USA.
Email: gsgoldman@roadrunner.com

pregnant women) cited by ACIP did not find increased childhood mortality associated with exposure to TIV in pregnancy.[3] However, fetal losses were not included in the analysis.

Based on the prior record of safety of TIV and the fact that the pandemic A-H1N1 vaccine shared the same licensure and manufacturing processes as the seasonal TIV, the ACIP recommended for the 2009/2010 influenza season that pregnant women receive the pandemic inactivated A-H1N1-virus vaccine in addition to the seasonal TIV (both produced by five approved vaccine manufacturers) during any trimester of pregnancy.

However, the safety and effectiveness of the pandemic (monovalent influenza) A-H1N1 vaccine had neither been previously established in pregnant women nor the combination of two different influenza vaccines ever tested in pregnant women. The A-H1N1 vaccine inserts from the various manufacturers contained this caution: "It is also not known whether these vaccines can cause fetal harm when administered to pregnant women or can affect reproduction capacity."

In October 2010, Moro et al. summarized that during 19 influenza seasons (1990/1991 through 2008/2009), there were a total of 17 spontaneous abortion (SAB) and 6 stillbirth (SB) reports following TIV in the Vaccine Adverse Event Reporting System (VAERS) database for an overall mean of 1.21 (23/19) fetal loss reports per year. This study's stated rate of fetal-loss reporting was 1.9 per 1 million (or 23/11,800,000) vaccinated pregnant women.[8]

In a second study published 8 months following the first, Moro et al. noted 121 SAB and 19 SB reports or a total of 140 fetal-loss reports to VAERS during the first 5 months of the 2009/2010 influenza season.[9] This equates to greater than 57 reports per million (>140/2,437,113) vaccinated pregnant women. The ratio of the 140 fetal-loss reports during the incomplete 2009/2010 season to the 1.21 reports/year representing the mean of the 19 prior seasons, yields a 116-fold (140/1.21) increase in fetal-loss reports (SAB and SB) in the VAERS database. Moro et al. attributed this dramatic increase, in part, to reporting bias, citing a "Weber-like effect."[9] The Weber effect is a temporal reporting pattern whereby the number of reported adverse events (AEs) for a new drug increases during the first 2 years of marketing and then subsequently declines, presumably reflecting decreased enthusiasm for reporting as AEs become well known.

Despite the statistically significant rate ratio (RR) of 29.4 (95% confidence interval (CI): 19.0–45.8) for 2009/2010 fetal-loss report rate (57 reports/1 million) to the mean rate of 1.9 reports/1 million (over the previous 19 influenza seasons), the second Moro et al. study concluded, " . . . H1N1 vaccination in pregnant women did not identify any concerning patterns of maternal or fetal outcomes."[9]

Was the increase in fetal-loss outcomes during the two-vaccine 2009/2010 influenza season merely the result of reporting bias or was there a synergistic toxicity associated with the two-dose 2009/2010 influenza season?

Methodology

Fetal-loss reports in the VAERS database for the two-vaccine 2009/2010 influenza season were compared with those reports from the immediately prior (2008/2009) and subsequent (2010/2011) single-vaccine seasons. The incidence of fetal-loss reports per 1 million pregnant women vaccinated was estimated for each season with 95% CIs computed based on the Poisson distribution. The RR of the fetal-loss report rate and CIs for the two-dose 2009/2010 influenza season to the fetal-loss report rate in the adjacent seasons were similarly estimated.

Independent survey of fetal loss related to 2009/2010 A-H1N1 vaccine

An independent survey was conducted by the National Coalition of Organized Women (NCOW) via the Internet to serve as a second surveillance source for pregnant women suffering A-H1N1 fetal loss during the two-vaccine 2009/2010 influenza season. Eileen Dannemann, director of NCOW, oversaw this study and the data collected are summarized in the Results section. In response to a public service announcement delivered via several websites on the Internet, respondents contacted one of two study coordinators via phone or e-mail address. The respondents provided relevant details including (a) type of influenza vaccine received, (b) date of vaccination, (c) type of vaccine, (d) date of onset of symptom/symptoms, (e) date of SAB or miscarriage, (f) geographic location, (g) whether or not the AE was reported to VAERS, and (h) other miscellaneous comments.

Capture–recapture analysis was used to determine the reporting completeness of fetal-loss reporting using two ascertainment sources: (1) the NCOW survey and (2) the VAERS database. Ascertainment-corrected fetal-loss report rates are computed by applying two-source capture–recapture methods to

Table 1. Comparison of fetal losses reported to VAERS for three consecutive influenza seasons, 2008/2009, 2009/2010, and 2010/2011.

	TIV 2008/2009 season	Additional monovalent A-H1N1 vaccine 2009/2010 season	TIV 2010/2011 season[a]
A. No. of pregnancies[b]	5,200,000	5,200,000	5,200,000
B. Approx. percentage vaccinated	11.3%[17]	43%[c]	32%[18]
C. No. of pregnant women vaccinated (A•B)	587,600	2,236,000	1,664,000
D. No. of fetal losses from VAERS	4	174[d] (152 A-H1N1 only + 18 A-H1N1 and TIV + 4 TIV only)	21
E. Incidence of reported fetal losses per 1 million pregnant women vaccinated (D/C)	6.8 (95% CI: 0.1–13.1)[e]	77.8 (95% CI: 66.3–89.4)[f]	12.6 (95% CI: 7.2–18.0)
F. RR of 2009/2010 season to adjacent flu season	11.4 (95% CI: 4.2–30.8)		6.2 (95% CI: 3.9–9.7)

VAERS: Vaccine Adverse Event Reporting System; RR: rate ratio; CI: confidence interval; TIV: trivalent inactivated influenza vaccine.
[a]The 2009 A-H1N1 strain, along with two seasonal strains (A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens) comprised the seasonal TIV in 2010/11, obviating the need for two separate vaccines.
[b]Number of annual pregnancies minus number of elective annual abortions = 6,408,000–1,210,000 is about 5,200,000.[16]
[c]National Health Family Survey (NHFS) reports 43% of pregnant women received the 2009 H1N1 vaccine (unpublished data from the Centers for Disease Control and Prevention (CDC)). This same figure is cited in the Moro et al. manuscript.[9]
[d]Shimabukuro reported 170 cases from VAERS, but did not include the entire influenza season. Shimabukuro T. Influenza Vaccine Safety Monitoring Update: Advisory Committee on Immunization Practices. Immunization Safety Office at the Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention (CDC). Presented on October 28, 2010. Slide #20 reports 149 SAB and 21 SB = 170 (unpublished CDC data).
[e]Moro et al. determined 5.5 million, but the denominator of the rate calculation included elected abortions.[9]
[f]Moro et al. determined 57.0 per million; however, the numerator of the rate calculation included case reports for only a partial influenza season and the denominator of the rate calculation included annual elective abortions.[8]

the number of reported fetal-loss incidents.[10–12] The estimator N^* of the total fetal-loss incidents is given by $N^* = [(b + 1)(c + 1)/(a + 1)] - 1$, where a is the number of fetal-loss incidents reported by both ascertainment sources, and b and c denote the number of fetal-loss incidents reported by the NCOW survey and VAERS ascertainment sources, respectively. When $a > 6$, there is 95% confidence that the theoretical bias is negligible; however, this does not account for any bias that might result from source dependencies or heterogeneity of the population within an ascertainment source.[13,14]

Since the distribution of the capture–recapture estimate is skewed in practice, to avoid misleading results associated with standard error estimates of result uncertainty, goodness-of-fit–based CIs were utilized.[15]

Number of annual pregnancies and percentage of vaccinated pregnant women

The number of pregnancies given in Table 1 for each of the three consecutive influenza seasons was derived from Ventura et al. and was presumed to remain relatively constant at about 5,200,000.[16] While this same reference was used by Moro et al.,[8] his figure of 6,408,000 pregnancies per year included about 1,210,000 elective annual abortions.

The 11.3% (for 2008/2009) and 43% (for 2009/2010) uptake percentages for pregnant women vaccinated shown in Table 1 were taken from the National Health Interview Survey (NHIS)[17] and an unpublished National Health Family Survey (NHFS), respectively. These percentages are cited by Moro et al.[8,9] A recent 2012 Centers for Disease Control and Prevention (CDC) report confirms the 43% uptake percentage during the 2009/2010 influenza season by reporting coverage among pregnant women as 47.1% for seasonal and 40.4% for A-H1N1 vaccine (mean 43.75%).[18] The 32% uptake percentage for pregnant women vaccinated in the 2010/2011 influenza season was reported by the CDC (and does not include the percentage of women vaccinated prior to or after pregnancy).[19]

Qualitative and quantitative assessment of trends in fetal-loss reports

The VAERS reports were examined for evidence of temporal or location clustering. In addition, the rate of fetal-loss reported per million population by state was assessed to determine any trends in reporting

Table 2. Comparison of mean time from vaccination to fetal demise and mean gestational age at fetal demise for VAERS reports and the NCOW survey, 2009/2010 influenza season.

	VAERS reports, $n = 174$		NCOW survey, $n = 67$	
Description	Mean	Number of respondents	Mean	Number of respondents
Elapsed time from vaccination to fetal demise	11.8 days (range 0–66)	166 (95%)	7.6 days (range 1–75)	57 (85%)
Gestational age at fetal demise	13.4 weeks (range 4–39)	113 (65%)	12.8 weeks (range 1–39)	56 (84%)

VAERS: Vaccine Adverse Event Reporting System; NCOW: National Coalition of Organized Women.

rates by state adjusted by population for the 2009/2010 influenza season. Also, fetal-loss reports due to seasonal TIV vaccine and percentages of female reports to total VAERS reports were compared for each of the three consecutive influenza seasons as well as two prior seasons in an attempt to discern and quantify any historical reporting trends or anomalies for the seasonal influenza vaccine adverse reports.

Quantitative estimate of factor of increased reporting potentially due to Weber-like effect

If no Weber-like effect existed, that is there was no increased or enhanced AE reporting associated with the newly marketed pandemic A-H1N1 vaccine during the 2009/2010 influenza season, we would expect the number of VAERS reports resulting from administration of the seasonal TIV and pandemic A-H1N1 vaccine to be approximately equal. In other words, the ratio of AE reports for A-H1N1 to seasonal TIV would be 1:1. Any increase in the number of VAERS reports associated with A-H1N1 over the seasonal TIV would yield a ratio or factor greater than one – representing the possible effect of a Weber-like reporting bias. Such a Weber or Weber-like reporting bias would expect to be generally distributed among all VAERS reports – not only those describing pregnant women experiencing temporally related fetal loss but also those describing other AEs among nonpregnant females and males. VAERS reports of anaphylactic shock occurring the same day of administration of influenza vaccine served as a control to test the potential Weber-like reporting bias.

Results

VAERS reports

Although there was an approximate fourfold (43%/11.3%) increase in the percentage of pregnant women vaccinated in 2009/2010 compared with 2008/2009, there was a 43.5-fold increase in fetal-loss reports – from 4 in 2008/2009 to 174 in 2009/2010. The report RR of 11.4 (95% CI: 4.2–30.8) of the 2009/2010 rate of 77.8 fetal-loss reports/1 million pregnant women vaccinated to the 2008/2009 report rate of 6.8 fetal-loss reports/1 million pregnant women vaccinated is statistically significant (Table 1).

Summary of the independent NCOW survey

The NCOW survey of fetal losses had a total of 72 respondents, 5 (7%) of which were excluded for the following reasons: 1 (1.4%) report of indirect H1N1 transmission to a child, which caused infection and miscarriage in a pregnant woman; 3 (4.2%) reports outside the United States (US); and 1 (1.4%) report with no adverse outcome. Of the 67 remaining instances, 62 (92.5%) and 5 (7.5%) reports of fetal demise were following A-H1N1 and seasonal TIV, respectively,

A comparison of the mean elapsed time from administration of influenza vaccine to fetal demise and mean gestational age at time of fetal demise is given in Table 2 for those of the 174 VAERS cases and 67 NCOW survey respondents that provided sufficient information. There was no statistically significant difference in the distribution of fetal loss by trimester between the VAERS reports and NCOW survey respondents ($\chi^2 = 1.69$; $p = 0.43$; Table 3).

Ascertainment-corrected reports for the two-vaccine 2009/2010 influenza season

Applying capture–recapture using 67 case reports from the NCOW survey, 174 case reports from VAERS, and 8 cases shared by both ascertainment sources, yields an overall reporting completeness for the two ascertainment sources of 17.6% based on an estimated ascertainment-corrected 1321 (95% CI: 815–2795) fetal-loss reports. Thus, the 174 VAERS fetal loss case reports represent 13.2% (174/1321) of

Table 3. Comparison of trimester of fetal demise for VAERS reports and the NCOW survey, 2009/2010 influenza season.

Trimester		VAERS reports, *n* (%)	NCOW reports, *n* (%)
First	(0–13 weeks)	74 (65.5)	40 (71.4)
Second	(14–27 weeks)	26 (23.0)	13 (23.2)
Third	(>27 weeks)	13 (11.5)	3 (5.4)
Total reports		113[a] (100.0)	56[b] (100.0)

VAERS: Vaccine Adverse Event Reporting System; NCOW: National Coalition of Organized Women.
[a]113 (65%) of 174 total reports contained gestational date information; 62 (35%) did not.
[b]56 (84%) of 67 total reports contained gestational information; 11 (16%) did not.

the total estimated fetal loss reports in the US population. The ascertainment-corrected rate of 590 fetal-loss reports per 1 million pregnant women vaccinated (or 1 per 1695) is 7.6-fold higher than the uncorrected VAERS rate of 77.8 (95% CI: 66.3–89.4).

Qualitative and quantitative assessments of trends in fetal-loss reports

Through an inspection of the lot numbers and demographics of the individual 174 fetal-loss reports in VAERS for the two-dose 2009/2010 influenza season, there appeared no clustering of the reports. Only a few 'states' provide evidence of increased fetal-loss reports during that season. The three 'states' with the highest reporting rates were District of Columbia (five cases), Vermont (three cases), and Montana (three cases), with 8.3, 3.2, and 3.0 fetal-loss reports per million population, respectively. The three states with the lowest fetal-loss report rates were Texas (five cases), New York (three cases), and New Jersey (one case) with rates of 0.198, 0.154, and 0.114 reports of fetal loss per million population, respectively. The highest number of fetal-loss reports, 20, was from California, yielding a rate of 0.536 fetal-loss reports per million population.

Presuming no significant uptake variability among the states based on the agreement of CDC's 2010 ten-state estimate (46.6%)[20] and Moro's 2011 reporting for the entire country (43%),[9] the state-to-state reporting of fetal loss following A-H1N1 vaccination appears highly variable (Table 4). In fact, nine states (Connecticut, Delaware, Idaho, Louisiana, New Hampshire, New Mexico, North Dakota, Oklahoma, and Wyoming) representing a combined population of 20.5 million reported no influenza-vaccine–related fetal losses. Eleven states reported only one case: Alabama, Alaska, Hawaii, Mississippi, New Jersey, Puerto Rico, Rhode Island, South Carolina, South Dakota, Utah, and West Virginia. Ten states reported two cases: Arizona, Arkansas, Iowa, Kentucky, Maine, Minnesota, Nebraska, Oregon, Tennessee, and Vermont (Table 4).

The ages of the women in the fetal-loss reports indicated a reporting bias associated with older pregnant women (mean age 32 years) as has been previously observed.[8,9]

The percentage of females filing VAERS AE reports in 2009/2010 was similar to that of the previous 2008/2009 season, with 63.9% (12,061 reports/18,866 total reports) and 61.8% (3529 reports/5707 total reports), respectively. The RR of 1.03 (95% CI: 0.996–1.07) was not statistically significant. In the 2010/2011 season, the reporting percentage for females was 66.4% (6372 female reports/9602 total reports). Despite the increase in females filing AE reports, there were no unusual trends in the percentage of female adverse reports over the three consecutive influenza seasons, 2008/2009 through 2010/2011 (Table 5).

Inspection of all influenza reports of males and females (shown in bold in Table 5, column 3) associated with the administration of all influenza vaccines over five consecutive influenza seasons reveals what appears to be an underlying linear increase for seasonal influenza-vaccine–related adverse reports from 3123 reports in 2006/2007 to 9602 in 2010/2011 having a constant increase of 1642 ± 109 reports/year ($r^2 = 0.99$; Table 5). Similarly, restricting the reports to females, there again appears to be a linear increase from 2048 reports in 2006/2007 to 6372 in 2010/2011, having a constant increase in 1086 ± 111 reports/year ($r^2 = 0.97$; Table 5, column 4).

Quantitative estimate of increased AE reporting attributed to a Weber-like effect

The factor of increased reporting that might be potentially due to a Weber-like effect in the 2009/2010 influenza season is quantified by computing the ratio of 7734 females reporting AEs associated with A-H1N1 vaccine to the 4863 females reporting AEs associated with seasonal TIV (Table 5), yielding a 1.6-fold increase in the A-H1N1 AE reports. Based on this potential Weber-like effect, given 22 reports of fetal loss associated with TIV, we would have expected approximately 35 fetal-loss reports (actually

Table 4. Rate of fetal-loss reports by state for two-vaccine 2009/2010 influenza season.

State	Population (in millions)[a]	No. of fetal-loss reports	Rate (fetal-loss reports/million population)
Alabama	4.803	1	0.208
Alaska	0.721	1	1.387
Arizona	6.413	2	0.312
Arkansas	2.926	2	0.684
California	37.342	20	0.536
Colorado	4.939	5	1.012
District of Columbia	0.602	5	8.306
Florida	18.901	7	0.370
Georgia	9.727	5	0.514
Hawaii	1.367	1	0.732
Illinois	12.864	6	0.466
Indiana	6.501	6	0.923
Iowa	3.054	2	0.655
Kansas	2.864	4	1.397
Kentucky	4.351	2	0.460
Maine	1.333	2	1.500
Maryland	5.790	6	1.036
Massachusetts	6.560	13	1.982
Michigan	9.912	8	0.807
Minnesota	5.315	2	0.376
Mississippi	2.978	1	0.336
Missouri	6.011	5	0.832
Montana	0.994	3	3.018
Nebraska	1.832	2	1.092
Nevada	2.709	3	0.738
New Jersey	8.807	1	0.114
New York	19.421	3	0.154
North Carolina	9.566	8	0.836
Ohio	11.568	5	0.432
Oregon	3.849	2	0.520
Pennsylvania	12.735	6	0.471
Puerto Rico	3.989	1	0.251
Rhode Island	1.055	1	0.948
South Carolina	4.646	1	0.215
South Dakota	0.820	1	1.220
Tennessee	6.375	2	0.314
Texas	25.268	5	0.198
Utah	2.771	1	0.361
Vermont	0.630	2	3.175
Virginia	8.038	6	0.746
Washington	6.753	5	0.740
West Virginia	1.860	1	0.538
Wisconsin	5.698	6	1.053

[a]http://www.worldatlas.com/aatlas/populations/usapoptable.htm for the States; DC and Puerto Rico from www.cia.gov.
[b]Nine states reported no cases: Connecticut, Delaware, Idaho, Louisiana, New Hampshire, New Mexico, North Dakota, Oklahoma, and Wyoming.

1.6×22 TIV $= 35.2$ reports) attributable to a 'Weber-like' effect associated with the A-H1N1 vaccines. Thus, the magnitude of the observed possible Weber-like effect explains neither the 170 fetal-loss reports in VAERS nor the nearly eightfold increase (170 A-H1N1 fetal-loss reports/22 TIV fetal-loss reports) that was found.

Use of an independent control AE group to isolate and independently estimate the potential size of a true Weber-like effect

To further investigate the presence of a Weber-like effect, VAERS reports were searched for an obvious AE, anaphylactic shock (including anaphylactic and anaphylactoid reaction and shock), occurring on the day of administration of influenza vaccine – usually shortly after the dose is administered. A review of the VAERS database found 20 and 22 such reports during the single-dose 2008/2009 and 2010/2011 influenza seasons, respectively; whereas, 46 reports were found during the two-vaccine 2009/2010 season. Presuming no Weber effect bias and relatively equal uptake of the pandemic A-H1N1 vaccine and seasonal TIV in the 2009/2010 flu season, about 21 AE reports ((20 + 22)/2) should have been expected for each of the two (seasonal and pandemic) vaccination programs or a total of about 42 reports for the 2009/2010 influenza season. The difference of four reports ($46 - 42 = 4$) between the actual and expected anaphylactic shock reports indicates a potential Weber-like, increase-in-reporting bias of less than 10% associated with the A-H1N1 vaccination program.

VAERS reports of fetal demise following administration of A-H1N1 vaccine and TIV

A recently published CDC morbidity and mortality weekly report[18] indicated that 28.5% of pregnant women were administered with both A-H1N1 vaccine and TIV. Since approximately 43% of pregnant women received at least one influenza vaccine (Table 1), the majority of those vaccinated – 66% (28.5/43%) – received a dose of both types of inactivated influenza vaccines.

Since the TIV became available early in the 2009/2010 influenza season, it was initially administered first followed then by the subsequent administration of a pandemic A-H1N1 vaccine when those inactivated 2009 A-H1N1 influenza vaccines became available. This probably partially accounts for the high

Table 5. A comparison of United States VAERS reports during five consecutive influenza seasons, 2006/2006 through 2010/2011.

Season and vaccine (July–June)	All VAERS reports	All influenza reports[a]	VAERS female influenza reports[b]	% of VAERS female influenza reports (100•B/A)	No. of fetal-loss reports to VAERS
2006/2007 TIV	20,502	**3123**	**2048**	65.6	–[c]
2007/2008 TIV	26,117	**4205**	**2654**	63.1	4
2008/2009 TIV	22,579	**5707**	**3529**	61.8	5[d]
2009/2010 A-H1N1	32,877	12,300[e]	7734[f]	62.9	170[g]
2009/2010 TIV		**7671**[e]	**4863**[f]	63.4	22[g]
2010/2011 TIV	23,416	**9602**	**6372**	66.4	21

Note: The bold figures show existing trends for the Trivalent Influenza Vaccine (TIV) over several years and should not be confused with the figures for the special 2-dose 2009/10 Influenza season which includes the unique, separate dose of A-H1N1. Also, linear regression analysis was run on the figures shown in bold to show statistical correlation and annual existing trends in TIV reports. VAERS: Vaccine Adverse Event Reporting System; TIV: trivalent inactivated influenza vaccine.

[a]All influenza adverse reports for TIV by year demonstrate linear correlation (figures in blue), $r^2 = 0.99$.

[b]Female influenza adverse reports for TIV by year demonstrate a linear correlation (figures in blue), $r^2 = 0.97$.

[c]Not Reviewed.

[d]Includes one live virus–related fetal death.

[e]For 2009/2010, the combined A-H1N1 and TIV influenza reports total 19,971; however, 1105 duplicate reports must be deducted due to patients reporting receipt of both TIV and A-H1N1, yielding 18,866.

[f]For 2009/2010, the combined A-H1N1 and TIV female influenza reports total 12,597; however, 536 duplicate reports must similarly be deducted, yielding 12,061.

[g]Figure includes 18 VAERS fetal-loss reports specifying receipt of both A-H1N1 vaccine and TIV.

percentage – 87.4% (152/174) – of VAERS reports that only reflect a SAB or SB after A-H1N1 inoculation and low percentage of 2.3% (4/174) of VAERS reports that reflect an incident of fetal demise after only a TIV inoculation.

Discussion

Capture–recapture estimates can lead to inaccurate and sometimes misleading results if the underlying assumptions are not met.[21] In epidemiological investigations, ascertainment sources often display dependence and heterogeneity of capture probabilities.[22] The major question individuals ask regarding capture–recapture is 'Will capture–recapture give you the truth?' That is, will it provide an extremely accurate estimate of the fetal loss incidence rates? Simply answered, no – it will not. When capture–recapture techniques are not utilized, the estimates presented in most epidemiologic studies are extremely poor, missing 10–90% of the cases, with a high degree of variation.[10,11,23,24] Thus, often the disease incidence that is reported simply reflects the incomplete case ascertainment of the study and not the true incidence of the disease in the population. Therefore, the options are (a) not to use capture–recapture and report fetal loss from which the incidence rates are almost uninterpretable since such rates merely reflect the level of case ascertainment, (b) try to count every case of fetal loss, which is horrendously expensive and slow, or (c) utilize capture–recapture, which, depending on the degree to which the assumptions are satisfied, as a compromise, can be a reasonably accurate, quick, and inexpensive approach.

The estimated 13.2% reporting completeness of the VAERS fetal-loss case reporting is suggestive of a low fetal-loss reporting rate during the 2009/2010 influenza season rather than a high reporting completeness of AEs – such as might be caused by a Weber-like effect. Furthermore, the general level of reporting of fetal-loss reports was variable when adjusted by state population with 56% of states reporting 0–2 cases (mean 1 report/state) and 44% reporting >2 cases (mean 5.4 reports/state) with no clustering of reports. Moreover, the percentage of influenza vaccine–related reports to VAERS for females was similar for each of the consecutive influenza seasons. Finally, the fetal loss rate dramatically declined from 77.8 fetal-loss reports per million women vaccinated in the two-vaccine 2009/2010 season to 12.6 fetal-loss reports per million vaccinated in the following single-vaccine 2010/

2011 influenza season. All these results argue against a significant fetal-loss reporting bias associated with the two-vaccine 2009/2010 season.

Based on respondents' comments to the NCOW survey in the 2009/2010 season, it is likely that the ascertainment-corrected rate of 535 fetal losses per million pregnant women vaccinated represents a significant underestimate during the two-vaccine 2009/2010 influenza season since health care professionals explained to patients 'the benefits of influenza vaccination outweighed the risks.' Medical literature reporting the mean rate of '1.9 fetal losses per million pregnant women vaccinated' for the previous 19 single-vaccine influenza seasons based on counts of VAERS reports that were not adjusted for under-ascertainment,[8] likely contributed to this perception of safety. Because both patient and health care professionals relied on a historical profile that was incomplete with respect to assessing fetal-demise reporting, a possible link to fetal demise following administration of influenza vaccine/vaccines during 2009/2010 was rarely contemplated or was considered highly unlikely and thus, more often than not, not reported.

The ratio of the 12,300 AE reports associated with A-H1N1 vaccine to the 7691 due to TIV is 1.60, which is similar to the ratio of 1.59 using female AE reports (Table 5). If a Weber-like increase existed, a readily discernible AE, such as anaphylactic shock, should have generated at least a 1.6-fold increase in VAERS reports associated with the 'new' pandemic A-H1N1 vaccine; however, no such increase was found. This independent AE control group confirms that most of the observed 7.7-fold (170 A-H1N1 fetal-loss reports/22 TIV fetal-loss reports) increase in fetal-loss reports associated with the administration of the 2009 A-H1N1 vaccine appears to be attributable to some type of toxicity effect rather than a 'new vaccine' Weber-like reporting effect.

When one or more Thimerosal-containing vaccines, including some formulations of the seasonal TIV and pandemic monovalent A-H1N1 vaccines are administered to a pregnant woman, the fetus is also indirectly exposed to mercury. In the following paragraphs, several peer-reviewed publications highlight the concerns that this mercury exposure poses.

A study using rabbits injected with Thimerosal-containing radioactive mercury showed that from 1-h post-injection to 6 h, the level of radioactive mercury in the blood dropped over 75% while from 2 h post-injection to 6 h, there were significantly increased radioactivity levels in the fetal brain, liver, and kidney.[25] Thus, the rapid drop in blood mercury levels from Thimerosal injection is due to uptake by other organs of the body and not due to excretion.[26] Therefore, the implications by others of Thimerosal's safety based on shorter blood level half-lives[27] suffers from lack of a circumspect view regarding this process.

The linkage between Thimerosal and neurodevelopmental disorders is a concern because several studies have shown that children with autistic spectrum disorders (ASDs) have higher levels of mercury body burden than typically developing children.[28–33] In addition, there is a positive correlation between mercury body burden and severity of ASD symptoms.[34–36] Direct measurement of injury in the brains of children with ASD reinforce this finding; there is a significant dose-dependent positive correlation between oxidative stress markers (evidence of brain injury) and mercury levels in the brains of children with ASD.[37]

The amount of mercury that accumulates in any given fetus and the severity of its impact depend upon several factors in addition to the maternal mercury exposure due to injected Thimerosal-containing inactivated influenza vaccines. Dental amalgams in pregnant women contribute to increased mercury burden in the developing fetus and newborn.[38–40] Also, the maternal–fetal genetic background can modulate fetal exposure to mercury; thus, certain gene variants influence mercury toxicokinetics causing the variable susceptibility that is observed with respect to mercury toxicity.[41] This variation in genetic susceptibility, combined with factors of diet and antibiotic use, can synergistically enhance mercury toxicity[42] and effectively preclude establishment of a safe mercury dosing level for all individuals. Moreover, the 0.1 mcg/kg/day reference dose that the Environmental Protection Agency (EPA) established as safe based on oral ingestion of mercury is not applicable for injected Thimerosal via vaccination since injection bypasses the absorption protection provided by the gastrointestinal system (which is also apparently dependent on the manner in which the fish or other mercury-containing food is prepared).[43] thereby delivering more of the toxic dose of mercury administered into the body.

Finally, Thimerosal has been found to be toxic at very low levels. For example, Parran et al. examined the effects of Thimerosal on cell death in a human neuroblastoma cell line. Following 48 h of a single dose of 4.35 nanomolar Thimerosal (or about 0.87 mcg/kg of mercury) over 50% of cells were dead.[44]

Thus, it is biologically plausible that during the two-vaccine 2009/2010 influenza season, when pregnant women were administered two Thimerosal-containing

Table 6. Gestational age, mean weight, and multiple of the EPA's RfD using 50% exposure.

Trimester	Gestational age in weeks	Mean weight (kg)[a]	Multiple of the EPA's RfD[b] based on 1 mcg of Hg in the vaccine dose[c]	Multiple of the EPA's RfD[b] based on 25 mcg of Hg in the vaccine dose[c]
First trimester	≤8	≤0.001	≥5000	≥125,000
	9	0.002	2500	62,500
	10	0.004	1250	31,300
	11	0.007	710	17,900
	12	0.014	360	8900
	13	0.023	220	5400
Second trimester	14	0.043	120	2900
	15	0.070	70	1800
	16	0.100	50	1250
	27	0.875	5.7	140
Third trimester	28	1.01	5.0	124
	29	1.15	4.3	109
	30	1.32	3.8	95
	42	3.69	1.4	34

EPA: Environmental Protection Agency's; RfD: reference dose.
[a]Mean weights 8-16 weeks[45] and 27-42 weeks.[46]
[b]Oral RfD = 0.0001 mg/kg/day (or 0.1 mcg/kg/day) for ingested mercury presumably from 'methylmercury species.'[47]
[c]Multiple of EPA's RfD based on 50% exposure = (0.50 • V/W)/0.1 mcg/kg; where V = micrograms (mcg) of mercury (Hg) in the vaccine dose and W = mean weight of fetus in kilograms (kg).

influenza vaccines each delivering 50 mcg of Thimerosal (or 25 mcg of mercury per dose), the fetus' mercury dose exceeded the EPAs reference dose (0.1 mcg of mercury/kg/day). This overexposure could be a significant contributing factor to some of the reported SABs and SBs. Moreover, the mercury in injected Thimerosal-containing vaccine doses has been found to preferentially bioaccumulate in the fetal tissues.[25] Table 6 demonstrates that depending upon the gestational age, the safety level of mercury (as specified by the EPA's reference dose) may be exceeded by several thousand fold for an early developing fetus during the first trimester to a factor of just over 1 at full-term – even for a single reduced Thimerosal vaccine dose presuming only 50% of the mercury (0.5 mcg) bioaccumulates in the fetus (Table 6, fourth column labeled '1 mcg of Hg in the vaccine dose').

Recent studies have similarly described biologically plausible mechanisms associated with the synergistic toxicity associated with multiple vaccine doses administered to children aged <1 year.[48,49]

The bias in reporting of fetal loss by older women may be due, in part, to this cohort's previous experience with one or more normal pregnancies, free from maternal complications when they did not receive an influenza vaccine during pregnancy, and thus, having more birthing experience than younger, first-time pregnant women. Also, this cohort may have a higher body burden of mercury from the bioaccumulation of mercury from dental amalgams, diet, prior doses of Thimerosal-containing vaccines, and other drugs.

The Internet survey was self-administered, thus, the responses are subject to reporting error since pregnancy and vaccination status were not validated by a medical record review. There may also be selection bias since women without Internet access would be excluded from referencing the Public Service announcement (and the survey). Nevertheless, Internet panels have been useful as surveillance data sources for postseason evaluation of influenza vaccination among pregnant women.[19]

Conclusion

The 1.8-fold increase in female AEs reports to VAERS following administration of pandemic A-H1N1 vaccine relative to seasonal TIV in the 2009/2010 influenza season is too small of a Weber-like increased reporting effect to account for the more than 40-fold increase in fetal-loss reports. Thus, the concomitant administration of the seasonal influenza and pandemic A-H1N1 vaccines during 2009/2010 suggests a synergistic toxicity and a statistically significant higher rate of fetal loss reporting relative to the single-dose seasons. When capture–recapture is applied to the two-vaccine 2009/2010

influenza season, the ascertainment-corrected reports yield an estimated rate of 590 fetal-loss reports per 1 million pregnant women vaccinated (or 1 per 1695). Without additional ascertainment sources, it was not possible to determine the reporting completeness of fetal losses associated with the 2008/2009 and 2010/2011 seasons.

The VAERS rates of 6.8 and 12.6 fetal-loss reports per million women vaccinated for those single-vaccine seasons may provide health care professionals with a sense that influenza vaccines administered during pregnancy are relatively safe, when, in reality, these rates merely reflect the low level of case ascertainment associated with VAERS and thus, grossly underestimate the true rates encountered in the US population. Just because a single vaccine has been tested and considered safe does not imply there will not be a synergistic fetal toxicity effect associated with the administration of two or more Thimerosal-containing vaccines to a pregnant women and/or a synergistic toxicity effect from the combination of the biologically active components contained in concomitantly administered vaccines.

In addition, because of the order of magnitude increase in fetal-loss report rates, from 6.8 fetal-loss reports per million pregnant women vaccinated in the single-dose 2008/2009 season to 77.8 in the two-dose 2009/2010 season, further long-term studies are needed to assess adverse outcomes in the surviving children. Additional research concerning potential synergistic risk factors associated with the administration of Thimerosal-containing vaccines is warranted, and the exposure-effect association should be verified in further toxicological and case–control studies.

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