Don't Trust me, I'm a Doctor: AEFI and the Breakdown of Regulation

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In Europe the safety assessment reports on vaccines are filed confidentially with the regulatory authority namely the European Medical Agency (EMA). The Italian court of Justice Nicola Di Leo has recently ordered that the periodic safety update reports (PSUR) 15 and 16 on Infanrix hexa (combined Diptheria Tetanus and Acelluar Pertusis, Hepatitis B, inactivated Poliomyelitis and Haemophilus influenza type B vaccine) – the GlaxoSmithKline Biological Clinical Safety and Pharmacovigilance's report to the regulatory authority – be made public and this is now available on the internet, hereafter the Report.[1]

It affords a rare opportunity for the public to see first-hand what these reports contain and why there is need for secrecy. It also bears testimony to the lack of due diligence on the part of the EMA, charged with the responsibility for public safety – for accepting these reports filed by the manufacturers at face value without seeking answers to pertinent questions.

In this paper I will concentrate only on the reports of deaths as adverse events after immunization (AEFI) in the PSUR as an illustration of the breakdown of regulation and why everyone needs a healthy dose of skepticism.

SIDS as AEFI

Most deaths occurring early in life are attributable to mainly to such causes as infections, congenital defects, malignancies and accidents. Very seldom do apparently healthy children die without any evident cause and these are classified as SIDS (Sudden Infant Death Syndrome) and SUD (Sudden Unexpected Deaths) if the death occurs after infancy.

During infancy, a number of vaccines are administered and some events of unexplained deaths (SIDS-SUD) can occur in temporal association but not causatively related with vaccination (purely by chance). It is acknowledged widely that it is difficult to say whether a death soon after immunization is caused by the vaccine or is a coincidental event. Many analyses are carried out to investigate whether the associations of frequent unexplained deaths following a particular vaccine are causatively related. The PSUR does an Observed/Expected analysis of sudden deaths to evaluate whether the number of sudden deaths reported exceeds what can be expected as coincidence.

PSUR 15 and observed/expected analysis of sudden deaths (SD)

The PSUR Report documents the deaths that have happened within 20 days of vaccination. They then look at it against the expected deaths during this period. GSK estimated that of the 60,626,633 doses distributed, 90.6% of all recipients were under 1 year of age. About 54 million doses were administered to infants below 1 year and about 5 million doses were administered to children older than 1 year. They calculate that the incidence of sudden death was 0.454/1,000 live births under 1 year and 0.062/1,000 live births in the second year. They also apply a healthy vaccinee correction factor of 0.8.

Table 1: PSUR 15 Cumulative number of Observed/ Expected cases of Sudden Death following Infanrix hexa in the first and second year of life

Time since Vaccination	Observed (1st year) (days)	Expected	Observed (2nd year)	Expected
Less than 1 day	***10***	***54.7***	***1***	***1.98***
1 day	***20***	***109.3***	***2***	***3.96***
2 days	***33***	***164***	***3***	***5.94***
3 days	***42***	***218.6***	***3***	***7.92***
4 days	***49***	***273.3***	***3***	***9.9***
5 days	***50***	***327.9***	***3***	***11.88***
6 days	***50***	***382.6***	***3***	***13.86***
7 days	***51***	***437.3***	***4***	***15.84***
8 days	***52***	***491.9***	***5***	***17.82***
9 days	***54***	***546.6***	***5***	***19.8***
13 days	54	765.2	6	27.72
15 days	55	874.5	6	31.68
16 days	56	929.2	6	33.66
18 days	57	1038.5	6	37.62
19 days	58	1093.1	6	39.6

(Source: Table 24 The GlaxoSmithKline Biological Clinical Safety and Pharmacovigilance Report to Regulatory Authority PSUR 15, page 783 of 1271)

The 'cluster of deaths' paradox

The fact that rate of deaths is highest immediately after vaccination, and decreases rapidly after that, makes it very likely that the deaths are related to the vaccination episode. There were 42 [42 – 0] deaths in infants in

the first 3 days and only 8 [50-42] in the next 3 days. It is difficult to imagine that reporting bias of a catastrophic event like SIDS is responsible for such a big change in such a short time. These are otherwise unexplained deaths in healthy children Unexplained deaths will have been investigated by a competent forensic team and the immunization records will have been examined to check if the infant was up to date with its vaccinations or whether there was an element of neglect. Reporting bias has little role under these circumstances.

Exaggerating expected deaths

1. There are other serious problems with how the 'expected deaths' are calculated. The safety assessment document has used the number of doses of vaccine distributed as the denominator. This makes no allowance for wastages assuming all the doses of the vaccine distributed, have indeed been utilized.

2. There can be another argument against using this denominator: The Report (page 702) mentions that vaccination could vary between 1 and 4 doses per subject in accordance with local recommendations. It is estimated to be between 15,156,658 and 60,626,633 subjects were exposed to the vaccine. Most babies died with the first dose of vaccination. As each child is given up to 4 doses and they could die after any one of the doses (and you can die only once), perhaps it would be more appropriate to look at the number of deaths against the number of babies vaccinated (rather than the number of units of vaccine distributed). Three doses are given in the first year. The number of children vaccinated is one third of number of doses calculated under year 1, and the expected deaths should perhaps be one third of what was sent to the EMA.

The PSUR 16 expected/observed analysis: enlarging expectation to cover the observation

In the PSUR 16 report, Section 9.3.1.1 on pages 246-249 of the document deals with the Observed to Expected analysis. The explanation on the calculation is identical to that in the 15th PSUR cited except for this passage:

"It can thus be estimated that 75% of all recipients of Infanrix hexa were in their first year of life, and 20% were in their second year of life (5% were not attributable because the age at vaccination was unknown). Therefore the number of doses (since launch) was estimated to be 54.7 million in infants under 1 year and 14.6 millions over the age of 1 year. The estimate of the number of doses in the second year was suddenly pushed up from 9.4% in the 15th PSUR to 20% in the 16th report."

Table 2: PSUR 16 Cumulative number of observed and expected cases of Sudden Death following Infanrix hexa in children in their first or second year of life

Time since Vaccination	*Observed (1st year) (days)*	*Expected*	*Observed (2nd year)*	*Expected*
0	***16***	***54.4***	***2***	***1.98***
1	***29***	***108.8***	***5***	***3.96***
2	***42***	***163.2***	***6***	***5.94***
3	***50***	***217.6***	***6***	***7.92***
4	***57***	***272***	***6***	***9.9***
5	***60***	***326.4***	***7***	***11.88***
6	***60***	***380.8***	***7***	***13.86***
7	***62***	***435.2***	***7***	***15.84***
8	***63***	***489.6***	***7***	***17.82***
9	***65***	***544***	***7***	***19.8***
10	65	598.4	7	21.78
11	65	652.8	7	23.76
12	65	707.2	7	25.74
13	65	761.6	8	27.72
14	65	816	8	29.7
15	66	870.4	8	31.68
16	67	924.8	8	33.66
17	67	979.2	8	35.64
18	67	1033.6	8	37.62
19	67	1088	8	.39.6

(Source: Table 36 The GlaxoSmithKline Biological Clinical Safety and Pharmacovigilance 16th PSUR report to Regulatory Authority, Page 249 of 1271)

The expected deaths are in fact much higher than that which is observed - except in children under 2 years where 5 die in the first 48 hours where only 3.96 were expected to die according to their calculations.

The 16th PSUR report had doubled the estimate of those getting the vaccine after 1 year from 9.4% to 20% doubling the figures for estimated deaths. Had the PSUR 15 distribution of doses under 1 year and over 1 year been used for the 16th report, the observed deaths would have been double what was expected for the first 4 days and actual death would exceeded expectation in the first 7 days.

Table 3: Expected Death in 2nd Year of Life Using PSUR 15 and PSUR 16 Criteria

Time since vaccination (days)	Observed (2nd year)	Expected deaths if in the distribution of doses 9.4% were in their second year of life as in the 15th PSUR	Expected according to 16th PSUR assuming 20% used in the second year of life
0	***2***	***1***	***1.98***
1	***5***	***1.86***	***3.96***
2	***6***	***2.79***	***5.94***
3	***6***	***3.72***	7.92
4	***6***	***4.65***	9.9
5	***7***	***5.58***	11.88
6	***7***	***6.51***	13.86
7	7	7.44	15.84
8	7	8.37	17.82
9	7	9.30	19.8

The PSUR merely doubled the 'expected deaths' to better match observed deaths and the EMA did not seem to notice.

Evaluation of possible justifications

In the PSUR 15 it is reported 60 million doses of Infanrix had been distributed worldwide since its launch and 5 million doses were administered to children in over 1 year.

72 million doses of Infanrix hexa were distributed during the period covered by the 16th PSUR report and 24 million over 1 year. This will suggest that 9 million children over 1 year (the increase from 5 million of the 15th report to 14 million in the 16th report) were vaccinated with Infanrix Hexa during the year of the 16th PSUR. This is more than a third of the total doses distributed in the year (36.5% of all doses distributed in the period of reporting of the 16th PSUR). Even if every child given Infanrix hexa went on to have all 4 doses and 1 of the 4 doses was given to children over 1 year of age, this figure cannot reach 36.5% of all doses.

If one considers the change to 20% from 9.4% is a correction made for what was historically wrongly calculated at 9.4%, the figure of 20% is still not tenable. Countries like Italy advise only 3 doses and all the doses are given under 1 year.

No matter how one looks at it, the increase to 20% cannot be justified and it seems evident that the motivation for increasing the calculated numbers of those receiving vaccination after 1 year, was a desire to try and cover up the high deaths in children over 1 year of age in the week after receiving Infanrix hexa. It is clear that Infanrix Hexa caused more deaths than is expected by chance.

Conclusions

1. The reason for keeping safety data on vaccines confidential is prima facie, suspect. If indeed the vaccine were safe, the manufacturer has more to gain by making it public rather than cloaking it in secrecy.
2. As opposed to faith that demands unquestioning acceptance of what cannot be verified, science is fundamentally defined as findings open to scrutiny by anyone. If scientific data is the basis for regulatory clearance, any data that is not open to independent scrutiny (other than by the regulators, who may be lazy or biased) is not science and no different from faith.
3. The EMA did not show due diligence when it accepted in the PSUR 15 and 16 and 'expected death rate' in the first year which was three times the likely correct figure – wrongly using a denominator of exposures to vaccine instead of number of children receiving their first dose of the vaccine.
4. The cluster of deaths immediately after immunization did not raise alarm bells and it suggests the EMA merely accepted the interpretations of the vaccine manufacturer without applying its mind.
5. In the 16th PSUR the manufacturer GlaxoSmithKline Biological seems to have deliberately increased (doubled) the projections for expected deaths in the 2nd year to cover-up the excessive deaths observed in the first 7 days after vaccination. The vaccine manufacturer should have been held to account for this possible sleight of hand.
   The EMA has arguably been negligent of its duty as a regulator for allowing this to pass (in the 16th PSUR) and has thereby exposed numerous other babies unnecessarily to the risk of death. Opening such data to the public (as the courts eventually did) serves to overcome the limitations of the EMA, as it can benefit from independent external critiques.
6. We as doctors have been naïve to accept such reports on the safety of vaccines. Justifiably doctors are losing the trust of the public and in the process we are endangering public health.

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Notes:

[1] http://autismoevaccini.files.wordpress.com/2012/12/vaccin-dc3a9cc3a8s.pdf