COMMERCIAL IN CONFIDENCE
NOT FOR PUBLICATION

ARVI/86/1st Meeting
ARVI/86/4

COMMITTEE ON SAFETY OF MEDICINES
JOINT COMMITTEE ON VACCINATION AND IMMUNISATION

JOINT SUB-COMMITTEE ON ADVERSE REACTIONS TO VACCINES AND IMMUNOLOGICAL PRODUCTS

London School of Hygiene and Tropical Medicine
(University of London)

Keppel Street London WC1E 7HT
Telephone 01-636 8636 • Cables Hygower London WC1 • Telex 8953474

Dr Derek Zutshi
Room C718
Alexander Fleming House
Department of Health and Social Security
Elephant and Castle
London SE1 6BY

14th October 1985

Dear Derek

Enclosed are comments on the estimates of vaccination-associated SIDS as presented at the recent ARVI meeting. I hope they prove helpful.

Let me add that this is a complicated problem, but one that I would be interested to pursue in the future.

Sincerely yours

Encs: Comments on "note on the estimation of sudden...."

Copies: Dr M Graveney
Prof R W Gilliatt

BMS

IN CONFIDENCE

Comments on TABLED PAPER 1 (APPENDIX TO ARVI/85/34):

"Note on the estimation of sudden infant deaths expected to occur by chance after immunization."

by Paul E M Fine, London School of Hygiene and Tropical Medicine

EXPLANATORY NOTE

These comments relate to a "note" prepared by the DHSS Statistics Division on the number of SIDS cases expected to occur by chance within 24 or 48 hours of receipt of a vaccination, if there were no causal association between them:

COMMENTS

1. "Method Used"

I have found the logic of the basic equation

$$ED = I \times \frac{S}{D} \times \frac{d}{D}$$

somewhat difficult to follow, in part because of the wording of the definitions of the variables. It is only valid for periods of time during which at most one injection can be given, and these several estimates are then summed to give an estimate for a full year. The examples given in appendix A illustrate this.

More importantly, I believe that the d/D correction factor is inappropriate, and that a more valid basic formula would be simply

$$ED = \frac{I \times S}{D} .$$

A simple derivation follows.

Assume:

S = number of SIDS among 3 month olds, per year (= 241 for 1983).

B = number of births per year. Note that B also equals the total person-months of 3-month-old experience during a year (as all children born between October in previous year and October in this year will live their "third month" in this calendar year).

V = number of DPT vaccinations performed among 3 month old children during the year.

Then:

S/B = risk of SIDS death during third month of life

= the chance that any child will die of SIDS during its third month.

Contd

$\frac{S}{B \times 30.5}$ = risk of dying of SIDS within any given 24 hour period for any 3 month old child (nb 30.5 days per month)

$V \times \frac{S}{B \times 30.5}$ = Number of SIDS deaths expected among 3 month old children within 24 hours of vaccination

But:

using DHSS notation, $\frac{V}{B} = I$, and 30.5 = D;

and thus: $ED = \frac{I \times S}{D}$

Note that the effect of the correction factor d/D has been to reduce the estimated number of SIDS deaths within 24 hours of vaccination. (The d/D was introduced in the original note to correct for weekends etc., when no vaccinations are given. But it should be recognized that the clustering of vaccinations during weekdays has two effects - it decreases the probability of chance association on weekends; but it increases this probability during the weekdays. The effects cancel each other out.)

2. "Data Used"

"The proportions of children born in 1982 who were immunized by the end of 1983" is used as an estimate of I in the calculations. This estimate has certain problems:

a) As noted on pages 2 and 3, this estimate excludes children who began but failed to complete a course of 3 injections. To this extent it is an underestimate and will lead to an underestimate of the number of SIDS expected to be time-linked to vaccination.

b) On the other hand, this estimate is based upon courses completed by children who are on average 18 months of age. To this extent it overestimates the number of vaccinations received before the first birthday (See 3b, below).

3. "Assumptions made"

a) The assumption is made that SIDS is distributed evenly throughout the year. This is not valid, insofar as SIDS is recognized to be strongly seasonal, peaking in winter months and with a seasonal low in July-August. On the other hand, it may be noted that this seasonality of SIDS would not affect the expected associations between SIDS and vaccination if vaccinations were distributed evenly throughout the year. The problem arises if both SIDS and vaccinations have a seasonal pattern. In theory, two contrasting situations could then arise:

i) If vaccinations and SIDS have similar seasonal distributions, this increases the probability of chance associations between the two.

ii) If vaccination and SIDS have different seasonal distributions, this would decrease the probability of chance association between the two.

Contd

In a preliminary analysis of (unpublished) data, we (JA Clarkson and PEM Fine) have found that first DPT vaccinations are not uniformly distributed during the year, but are distributed approximately 28%, 26% 25% and 21% by quarter. Though we have yet to examine thoroughly the implications of this distribution, it may increase the expected number of chance associations between SIDS and vaccination during the previous 24 hours.

b) The note first assumes that vaccinations are given at recommended ages (examples 1 and 2) and then explores the implications of a slight delay ("slippage") in example 3. In a preliminary analysis of (unpublished) data on the ages at which infants actually do receive their DTP vaccinations, we find this "slippage" effect to be even more severe than that shown in the DHSS notes example.

For example, rather than 58% of infants receiving their initial DTP at either 3 (example 1) or 4 (example 4) months of age, our data suggest that approximately 18%, 17%, 8% and 7% of infants received their first DTP in their third, fourth, fifth and sixth months of life, respectively, in recent years. Given the fact that the risk of SIDS falls rapidly after the 3rd month of life, these delays in starting triple vaccination reduce the estimated number of SIDS occurring by chance within 24 hours of vaccination.

c) It is pointed out in the note that a substantial proportion of SIDS infants had symptoms prior to death which might have excluded them from vaccination. It may be worth noting that some of the non-medical, socio-economic factors associated with SIDS may also be associated with low vaccine uptake. The extent of these biases may be quite large, and deserves further investigation.

d) It should be recognized that example 2 given in the note relates not to DT vaccines per se, but to any vaccines including D and T antigens, thus including DTP. If we were to assume that all pertussis vaccine is given as DTP, then the expected number of SIDS cases to occur following DT vaccines per se, using the method applied in the note, would be 7.2 - 5.7 = 1.5.

CONCLUSION

These brief comments indicate a number of problems which arise in estimating the number of SIDS deaths expected to arise by chance, within 24 hours of a vaccination, if there were no causal association between them. Some of these problems favour overestimation and others favour underestimation by the method used in the DHSS note. Given the nature and direction of the biases, it is probable that the estimates presented in the DHSS note are of the correct order of magnitude. On the other hand, given the importance of the subject, a more thorough examination of the subject seems appropriate.