Graham, Laverne

From: Verstraeten, Thomas
Sent: Friday, December 17, 1999 4:40 PM
To: 'Robert Davis'
Cc: Destefano, Frank
Subject: It just won't go away...

Hi,
Attach please find four tables with RRs and three SAS programs:
Sumstat_alldia_sort (created by TH_anal_nonbob_expl3.txt) has the RRs after PH models adjusted for gender, site and birthyear for all diagnoses included.
Sumstat_alldia_sort2 has the RR for the conditions that came out to be relevant from the first list.
Sumstat_alldia_strat (created by TH_anal_bob_str) has the same after stratification for site, year and month of birth, adjusting for gender and leaving out the kids that got HepB immunoglobulines. It differs very little from the previous, except for the coordination disorders.
Sumstat_bob (created by TH_anal_bob_expl3.txt) has the RRs for the categories of diagnoses, adjusted, not stratified (I did it for one and got basically the same result).
In the lists you'll also see the sample size for each category and the referent category, some of which are quite small when making 4 categories, reason for using 3 slightly different categories with similar results (Hg3cat1 vs. hg4cat1 and hg3cat3 vs. hg4cat3).
I added another exposure variable (addcat) in one llist that looks at the increase of mercury each month for the first three months, divided by the average bodyweight in the first, second and third month and takes the maximum value of this. This does not show much, to which I would conclude that, except for epilepsy, all the harm is done in the first month.

As these neurologic developmental conditions are very much related (odds of having one when also having the other go from 20 to 100!), I added the first five (called mix) and checked what happened to the RRs. (You get some sort of average.) I will explore the possibility of some sort of factor analysis to replace the conditions by one variable.

As you'll see some of the RRs increase over the categories and I haven't yet found an alternative explanation... Please let me know if you can think of one. Frank proposes we discuss this on a call after NewYear.

Also attached my EIS abstract to get your input.

Happy holidays!

Thomas Verstraeten, M.D.
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On Wed, 19 Apr 2000, Verstraeten, Thomas wrote:

> Bob,
> Here are the samples in an Excel file.
> I have selected 10 non-premature, non-excluded (for congenital or perinatal
> disorders) infants using a periodic sample of 1/10 so as to maximize the
> diversity in years of birth.
> There are 10 infants with autism (2990), ADD (3140), Speech delay (31539)
> and unspecified developmental delay (3159)
> Added (free!) is a sample of 10 premature infants with 3159, which we have
> found at NCK to have a RR of 5 when comparing DTP-Hib separate vs combined.
> This finding is very extreme and would warrant closer examination of these
> diagnoses.
> I know I cannot check the same risk at your site, but the percentage of
> prematures among cases of 3159 is also exceptionally high at your site (22%
> vs 6% among cases of 31539)...
>
> Good luck and thanks!
>
> Tom.
>
> Please confirm receipt and whether or not this file gave you any problems to
> open.
>
>
> -----Original Message-----
> From: Destefano, Frank
> Sent: Wednesday, April 19, 2000 11:13 AM
> To: 'Robert Davis'; Destefano, Frank
> Cc: Verstraeten, Thomas
> Subject: RE: Summary of Chart Review
>
>
> Thanks again. We'll get this to you ASAP, but we don't have names here. We
> can send the studyid and dates.
>
> -----Original Message-----
> From: Robert Davis [mailto:rdavis@u.washington.edu]
> Sent: Wednesday, April 19, 2000 11:09 AM
> To: Destefano, Frank
> Cc: Verstraeten, Thomas
> Subject: RE: Summary of Chart Review
>
>
> Yes, Iwill make it possible even if I have to do it myself. If you can get
> me the studyids I will send in the chart request slip today (if you can
> give me the name and any other identifying info as well that would be
> great; esp helpful would be the date of the diagnosis- that way I can

Graham, Laverne

From: Boyle, Coleen
Sent: Tuesday, April 25, 2000 3:55 PM
To: Destefano, Frank
Cc: Sinks, Tom
Subject: comments of analysis

Frank: Just a few comments from yesterday's presentation:

General comment: Given the complexity of the analysis, it would be helpful to me to have more information on the cohort -- basic descriptive statistics.

1. how consistent were the findings by various subgroups -- e.g. between HMOs, race groups, gender, etc.

2. Since most of the dx's are generally not picked up until the 2nd or 3rd year of life had you considered eligibility criteria of at least 18 months or 2 years?? What happens if you do this?

3. Show analyses with and without perinatal/congenital conditions deleted (by eliminating the premature kids you have already excluded those at greatest risk of a DD.)

4. Early dx of these disorders is strongly associated with SES -- can you control for your marker variable of SES (Not sure if SES is related to thimerosal, but surely compliance with vaccination schedule.)

5. For me the big issue is the missed cases -- and how this relates to exposure. Clearly there is gross underreporting -- 1.4% of the kids dx'ed with a speech and language problem vs. 4-5% from reported in national surveys; <1% with ADHD vs 3-10% reported previously; etc.

6. There seem to be small numbers in the none and low exposure groups -- how do the characteristics of these groups differ from the higher exposure groups

7. Just a note: your case definition slide does not match what are presented in the tables.

Hope this is helpful -- let me know if there is anything else I can do.

thx

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> -----Original Message-----
> From: Destefano, Frank
> Sent: Wednesday, April 19, 2000 11:13 AM
> To: 'Robert Davis'; Destefano, Frank
> Cc: Verstraeten, Thomas
> Subject: RE: Summary of Chart Review
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> -----Original Message-----
> From: Robert Davis [mailto:rdavis@u.washington.edu]
> Sent: Wednesday, April 19, 2000 11:09 AM
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> Cc: Verstraeten, Thomas
> Subject: RE: Summary of Chart Review
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From: Robert Davis [rdavis@u.washington.edu]
Sent: Sunday, April 23, 2000 1:03 PM
To: Verstraeten, Thomas
Cc: Destefano, Frank
Subject: Re: Samples for Chart Review

Of the 10 charts we requested, 8 were obtained and 2 are in archives (and
are unavailable, at least today)

I reviewed the 8 and assessed them for the following characteristics
-Final diagnosis
-Age when first diagnosis was made (I thought this would be useful if we decide to expand the chart review, since it would provide the 'lowest' age that we might allow children to be included in the study)
-Age at last follow up
-A listing of the range of types of medical personnel involved in making the diagnosis at one time or another
-A subjective assessment, by me, of the certainty of the diagnosis. I did this in order to help us recognize those diagnoses that are 'possible', or 'rule-outs'. However, to my surprise, _every single one_ of these diagnoses had a certainty level of "High". That is, they were all seen by multiple providers (including neurology, psychology, speech and lang etc), with little (if any) disagreement noted with regards to the diagnosis.

The final diagnosis was: Autism in 7. The eighth child had a diagnosis of pervasive developmental disability specified only (no specific mention of autism).In addition, 3 were noted to have features of ADD. Only one had a specific diagnosis of speech delay but all were seen repeatedly by speech and language, so I think that the speech delay was not mentioned separately since it was such an integral part of their autistic spectrum.

The ages when the first diagnosis were:

2 y 1 mo
2 y 2 mo
2 y 5 mo
2 y 6 mo
2 y 6 mo
2 y 9 mo
3 y 3 mo
3 y 6 mo

The ages at last follow up were:

4 y 10mo

4 y 11mo
5 y 6 mo
6 y 2 mo
6 y 4 mo
7 y 2 mo
7 y 5 mo
8 y 0 mo

In terms of who was involved in making the medical diagnosis, I was impressed with the extent of evaluation and the number of physicians and other personnel who saw each child. All were seen by a center for Speech
and Language Evaluation where they underwent extensive evaluations (although, as noted previously, there is a lack of 'quantitative testing'). All but one was seen by neurology. ALl were seen by the occupational therapy services department. At least 2 were also seen by Geri Dawson at CHDD and one was on the secreting study. Hence my feeling
that the certainty of diagnosis is high.

I hope this helps. My interpretation of this admittedly small review is that a study based on chart review would probably be able to confirm that
these children had real diagnoses, rather than simply evaluations for possible problems or rule-out problems. I was struck by the % of these that had formal diagnoses of autism. Many - but not all- of these had enough formal documentation such that even if we brought in a set of outside reviewers to confirm the diagnosis I think that many of these charts would be accepted (that is, children noted to have atypical stereotypical behavior, hand flapping, fascination with minute detail and
extreme frustration when these objects are taken away, etc)

Im not sure what we would find if we looked at children with'just' developmental delay, or 'just' speech delay, so I cant really draw any conclusions about that. However, I do think that Tom's point (that these children are being brought in for _something_, and that this is unlikely to bear any a-priori relationship to their likelihood of receiving some level of thimerosal in the first 3 months of life) is a very good one.

Bob

ps Tom, can I get a copy of your powerpoint slide presentation to the EIS
conference? The reason I ask is that I am putting together the poster for
the national pediatric conference, and especially with all this now going
on, I want to make sure that I dont say anything that goes beyond what youve already said publicly. Okay?

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> focus the chart reveiw
> Bob
>
> Robert L. Davis, M.D., M.P.H.
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>
> On Wed, 19 Apr 2000, Destefano, Frank wrote:
>
> > Thanks, Bob.
> >
> > This information is helpful. It would be useful to also have a
sense of
> > what the charts reveal for some of the key diagnoses in the
automated
> data.
> > Would it be possible by next Monday or Tuesday for you to review say
5-10
> > charts for each category of interest (i.e., developmental speach
delay,
> ADD,
> > autism) to see what the actual diagnosis and status (?severity) was?
If
> > this is possible, Tom should be able to provide you with a random
sample
> of
> > studyids.
> >
> > -----Original Message-----
> > From: Robert Davis [mailto:rdavis@u.washington.edu]
> > Sent: Tuesday, April 18, 2000 5:37 PM
> > To: DeStefano, Frank (NIP); Verstraeten, Thomas
> > Subject: Summary of Chart Review
> >
> >
> > Tom and Frank
> > I pulled the following from my notes. I looked at 12 charts total.
My
> > memory of how I chose to choose the charts was not quite correct: I
did
> > not use the ICD-9 codes but instead pulled the charts of 2 children
for
> > each of 6 CPT procedure codes. I now remember the reasoning behind
this,
> > which is that I thought that finding children with 'procedures' such
as
> > standardized testing _might_ help us identify children for whom some
> > quantitative measure or set of measures existed.
> >
> > The CPT procedure codes were as follows:
> > 96100 psychological testing
> > 95882 cognitive testing
> > 95883 neuropsychological testing
> > 96117 neuropsychiatric test battery
> > 96111 developmental testing, extensive

> > 96110 developmental testing, limited
> >
> >
> > There is no easy way to summarize exactly what I found, but I will try.
> >
> > For the children who had psychological testing (96100), one had a notation
> > of getting an MMP (Minnesota Multiphasic Personality test) and a MCAC (I
> > dont know what this acronym is) done, but there were no results in
> > the chart. (Some of these evaluations are kept at the Mental Health
> > Center where the test was administered; we would need human subjects
> > approval re: a formal study in order to look at that record,
> > unfortunately). The other child with this CPT code did not have any
> > record of the test restults in his chart.
> >
> > For children with 95882, Cognitive neuropsych testing, the chart only
> > stated 'long standing autism'; there was no record of formal neuropsych
> > testing. The other child with this code had the following tests
> > administered: Woodcock-Johnson psychoeducational battery; analytic
> > reading inventory; peabody picture vocabulary test; detroit test
> > learning aptitude test; photo-articulation test; and then on
> > another date had: Wechsler Intelligence Scale; wide range
> > achievement test; test of written language; halstead reitan
> > neuropsych. test battery for children 9-14 years; and the selective
> > reminding test.
> >
> > For children with 95883: for one there was no record of formal
> > testing, for the other , he had clinical evaluation of receptive and

> > expressive language; bracken test of basic concepts; peabody picture

> > vocabulary test; token test for children; expressive one word
> > picture vocabulary test; length of utterance test.
> >
> > For children with 96117: One had PPVT; Woodcock-Johnson; Perceptual
> > speed test; tests of problem solving; and tests of audicatory
> > perceptual skills; the other had no record of formal testing.
> >
> > For children with 96111: on ehad a brief physical therapy motor
> > evaluation, and the other had a history of prematurity, respiratory
> > distress syndrome after birth, low birthweight, and had peabody
> > developmental motor scales done.
> >
> > For children with 96110: one had speech and language evaluation and
> > a denver developmental screening test and a diagnosis of autism and
> > pervasive developmental delay. The other had no record of formal
> > testing.
> >
> > I hope that this gives you some flavor of the enormous variability in data
> > type as well as data availability. I think that the best we could do is
> > come up with some crude measure of the fact that the child was, in fact,
> > evaluated and _maybe_ some very basic assessment by the doctor that
> > the child was - in fact - not 'normal'. HOwever, I doubt that we
> > would be able to tie some specific doctors notes to the ICD-9