The Signature: A Never-Sent Letter to the Editors of Neurology, Updated With Commentary and Guidelines for the Future

Benjamin M Blumberg
Department of Neurology, Microbiology and Immunology, University of Rochester Medical School, NY, USA

Corresponding author: Benjamin M Blumberg, Former Associate Professor, Department of Neurology, Microbiology and Immunology, University of Rochester Medical School, 6 Horizon Rd, Apt 2302, Fort Lee, NY, 07024, USA, Tel: +1 555-275-2100; E-mail: bbrl@aol.com

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Letter to Editor

The Original Letter, Not Sent in 2009

Sirs,

A recent paper in Neurology by Annette Schrag et al. [1,2] with an accompanying editorial by D.L. Gilbert and R. Kurlan [2] caught my attention as being a perfect example of what modern medicine is doing, right and wrong in its current policies regarding the statistical treatment of patient data. Schrag et al. did a magnificent job surveying a database of 678,862 UK patients to search for associations between streptococcal infection and certain neuropsychiatric disorders including tics, Tourette syndrome and obsessive-compulsive disorder collectively termed PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus B infection; Swedo et al. [3]). Schrag et al. [1] used conditional logistic regression to identify controls matched for age and sex and wound up with 254 cases and 2,211 controls. They sliced and diced this data for such other variables as antibiotic treatment and ethnicity, but in the end could not confirm a statistically significant association between streptococcal infection and the PANDAS [1].

So are we to believe that there really is no association, or is there something wrong with the statistics? Clearly the authors still think there is an association, because in comparing their results against an older USA study [4] which found twice as high an association, they were unable to point out specific reasons for the different findings [1]. They went on to say that only a prohibitively expensive prospective study with high diagnostic accuracy and laboratory confirmation of streptococcal infection could overcome this problem [1] – but then cited a more recent, prospective US study of exactly this type [5] in which the degree of association was also found to be vanishingly low.

Similarly, there is much anecdotal evidence that administration of the MMR vaccine to infants and children below 3 years of age is often followed closely by reversal and loss of developmental landmarks and abilities related to socialization, i.e. by the development of autistic syndrome disorder (ASD). Remarkably, we are currently in the midst of an autism epidemic, in which one in fewer than 100 children presents with ASD following exposure to a vaccine or environmental agent, yet studies using population-based statistics show no difference in ASD incidence between children who received the MMR and those who did not [6].

I think that there is indeed something wrong with the use of population-based statistics in these two cases. The original suspicions of an association between streptococcal infection and the PANDAS were based on a close temporal relationship between the onset of infection and the development of the disorder, and were supported by the clear correlation between neuropathologically identified infection of the basal ganglia and its neuronal projections to target areas [7]. The situation is analogous to the well-known association of immunoreactivity to streptococcal infection in the case of rheumatic heart disease [8]. Similarly, the close temporal relationship between infection with measles virus (part of the MMR) and ASD is ignored, despite the well-known role of measles virus in causing neurological diseases such as sub-acute sclerosing panencephalitis (SSPE) [9].

I assert that when population-based statistics are used in an effort to demonstrate an association between a disorder and a suspect agent, and the signal goes away, this is in fact the signature of either a multiagent infection, or an infection with an agent that can take on multiple forms and functions, or a ubiquitous commensal agent, and that population-based statistics are simply not appropriate for analysis of such disorders, because the temporal data are ignored and thrown away. Unfortunately, the appropriate mathematics for recognizing and analyzing multiagent diseases are currently lacking, but could be constructed using algorithms that give due weight to the temporal relationships.

We are living in a post-Koch's postulates age, where important diseases of unknown etiology are becoming rare. The agents of a few new diseases, such as Lyme disease, MERS and SARS, have been identified by classical methods, but probably the majority of well-known diseases of unsolved etiology nowadays are caused by multiple viruses and ubiquitous commensal form- and function-shifting bacteria. The problem of population-based statistics is that in certain cases where the temporal relationship is strong but the neuropathological correlate is lacking, our inability to identify the agent tends to close off investigation and debate. Perhaps a fresh look at etiology in Autism Syndrome Disorders, the PANDAS and ALS (Lou Gehrig's disease) will serve as models for relieving this statistical impasse.

Commentary on the Letter, Updated for 2016

A search of PubMed for PANDAS (10/27/2016) reveals that the current status of the association of Streptococcus B agents with tics, Tourette's syndrome and OCD is still uncertain. The symptoms of PANDAS-type disorders are now being treated by procedures as disparate as antibiotic prophylaxis, ticsollectomy, plasmapheresis, and especially manipulation of the patient's immune status with IVIG [10-14]. Each of these measures has had some limited success, but none can reliably treat a random patient, and none has really addressed the cause of the disorders: the suspected Streptococcus pyogenes bacteria [10-14].

Our understanding of the capabilities of these bacteria is still expanding, and we now consider ourselves in the post-antibiotic age,
where bacterial resistance to the antibiotics that did so much to make
the practice of medicine seem like magic in the years from the 1930s
through the 1990’s is now becoming common. *Streptococcus pyogenes*
spp. have the ability to resist antibiotics in at least five ways: by
generating enzymes that inactivate the antibiotics; by modifying their
cell walls so as to exclude the antibiotics from entering the bacteria; by
adopting metabolically inert forms that resist the action of the
antibiotics; by hiding out inside infected cells in persistent forms that
do minimal damage to the cells; and also by co-operatively generating
a biofilm and hiding under it, thereby avoiding contact with the
antibiotic [7,15]. Faced with such a formidable and devisous bacterial
armament, it is no surprise that the PANDAS and their statistics are
still in flux.

The situation regarding the relationship between administration of
the MMR vaccine and acquisition of autism in vaccinated children is
quite different. Here, it turns out that there is a close relationship after
all, but it has been concealed from the public by the CDC in the
interests of VICAP, the government program meant to reimburse the
families of infants injured by vaccines, and thus protect the vaccine
manufacturers. The CDC concealed the connection by fiddling their
numbers, so no matter how sophisticated the mathematical treatment
of the data, as required by Neurology’s new standards, the results
would still be cooked. This government malfeasance was recently
revealed by a whistleblower at CDC, Dr. William Thompson. The story
has been all over the Internet for a while, and recently it has been
published in the *Townsend Letter* [16,17].

Remarkably, this fiddling of data combined with the assertion that
studies using population-based statistics show no difference in ASD
incidence between children who received the MMR and those who did
not has buffleoded some of the brightest minds in America. In a brief
conversation with Dr. Thomas R. Insel, head of the NINDS, at a NYAS
meeting in 2014, I asked him why nobody had found a connection
between the MMR and autism, and he responded reflexively with the
“no difference in ASD incidence” argument.

**Guidelines for the future - Magic overcomes outrage!**

So where do we go from here in regard to the statistical
conundrums of the PANDAS and the MMR/autism controversy? Neurology was under the chief editorship of Dr. Robert Griggs when
the new standards for mathematical rigor were instituted. Now it is
under the chief editorship of Dr. Robert Gross, who recently presented
an article on medieval medicine in Saudi Arabia that showed, on the
cover of the Sept. 6 volume, pins inserted through the suture lines of a
skull to relieve epilepsy symptoms in a patient. I took Dr. Gross to task
for this article [18], which wondered “whether the demon was
successfully expelled”, as not being appropriate as a model for modern
neurological practice, but perhaps I was wrong. It now occurs to me
that the best ways out of the conundrum and controversy above, may
indeed be by expelling the demons, i.e., by magic. Even Dr. Paul Offit,
in his book  “Autism’s False Prophets”, refers to magic in medicine in a
quote from Thomas Szasz:

> “When religion was strong and science weak, men mistook magic
> for medicine. Now, when science is strong and religion weak, men
> mistake medicine for magic.”

The magic I would commend to your attention for treatment of the
PANDAS is the Marshall Protocol [19,20]. This protocol was used by
Dr. Trevor Marshall to cure his own case of sarcoidosis, and he thinks
it applies to all Th1-type bacterial infections. The Marshall Protocol has
been available on the Internet for several years, but has not gained
nearly as much traction as it deserves. The reason, I think, is that the
underlying disorder is one of those exponential problems that crop up
occasionally in biology, and is difficult for the unprepared mind to
visualize.

To help visualize it, think of the old problem of the Indian Prince
who loves the Princess but is required to place 2x grains of sand on the
64 squares of a chessboard, where x=0 (1 grain) for the first square,
x=1 (2 grains) for the second, x=2 (4 grains) for the third... etc., to win
her hand. Around the 35th square, not all the dump trucks in the
world can carry the required amount of sand. A different way to look
at this is the old lily pad on a pond problem - here the element of time
enters. If a lily pad growing on a pond doubles in size every day, on
which day will the pad occupy half the area of the pond? The obvious
answer is: on the next-to-last day - but when the last day may come is
the serious part of the question.

The protocol itself [19] can be described as alternating doses of an
antibiotic, usually a broad-spectrum antibiotic at first, followed by the
drug benicar (Olmesartan). Each round of treatment thus consists of
antibiotic/benicar, and can be visualized as one turn of a crank. The
antibiotic kills some of the bacteria, but not all, and the survivors then
drop one or more of the various means of resistance noted above, and
are held in this resistant state by the innate immune system. The drug
benicar is an antagonist of the Vitamin D receptor which controls the
innate immune system, so treatment with benicar releases the bacteria
to grow again and thus again become susceptible to the antibiotic. The
problem here is that each turn of the crank takes about two weeks: one
week for the antibiotic to work, and a second week for the benicar to
take effect. If only a small fraction of the bacteria are killed with every
turn of the crank, it may take many turns of the crank - say, 50 turns =
2 years - before the infection even begins to be controlled. There are
probably few physicians who would be willing to continue this
protocol for 2 years before any results are noted, which is why it is not
yet widely accepted. But that is the magic - you have to keep the faith,
baby.

In practice, the protocol is somewhat different, of course. Treatment
actually consists of a constant dosage of benicar, punctuated by doses
of antibiotics. The antibiotics can be varied and optimized during the
course of treatment, to reflect laboratory findings on the bacterial
strains involved. But the charm of the Marshall Protocol is that it will
work in most cases without exact advance knowledge of the causative
agent. The benicar treatment makes life under treatment difficult,
because all sources of Vitamin D must be restricted, including sunlight.
This is somewhat balanced by the possibility that the Marshall Protocol
may work on other difficult-to-treat disorders besides the PANDAS, such as ALS and Lyme disease.

Finally, what magic can be used to fight a reluctant Federal
Government and rationalize the administration of vaccines so that the
present (wholly unacceptable) incidence of 1/68 children who acquire
ASD can be brought back to its level of 4/10,000 as of 20 years ago?
Here, the magic is just two words: "Reporting Period". Currently, the
reporting periods for autism, as noted in the whistleblower’s report are
16, 17, 18 and 36 months. That is, data is collected every 1 or 3 years on
which children received the MMR and other vaccines, and which
children did or did not develop an ASD of some sort. Under the
current guidelines of the American Pediatric Association, at least 12
vaccines are given, some in repeated doses, to infants and toddlers
between the ages of 1 and 3. This means that every two to three
months, a dose of vaccine is given, often enforced by school
restrictions for the children of those parents who object to this heavy vaccination schedule. In my opinion, it is the mismatch between the short vaccine intervals (at least one dose every 2-3 months) and the current lengthy reporting periods (1-3 years) that causes the statistical error that ignores the temporal relationship between vaccination and onset of autistic disorder. If the Reporting Period were made shorter, every 2-3 months, consistent with the vaccination schedule, the association between vaccination and disease onset would stand out a mile, and then the debate about whether and which vaccinations cause autism could proceed on a rational basis.

By far the best books on the MMR/autism problem were written by Dr. Paul Offitt, the inventor of the rotavirus vaccine among other accomplishments. When Dr. Offitt’s first book “Autism’s False Prophets” was first published, I sent him a letter telling him that he was wrong about there being no connection between the MMR and onset of ASD. This was perhaps not the best way of introducing myself, and I did not hear back from him, but now I know what I did not know in 2008: the magic words "Reporting Period", which form a sort of bridge between a bench scientist like myself, the pediatrician (and vaccine developer) Dr. Offitt, and the epidemiologists and statisticians like Dr. Walter Zaharodny who derived the outrageous but probably correct figures of ASDs now being acquired by one in 68 children [21]. Perhaps if I had told Dr. Offitt that he had ignored the importance of the mismatch between the reporting period and the pediatric vaccination schedule, he would have understood. Hopefully, you, the reader, will now understand.

"Autism’s false prophets" was all about the ways in which a federal government bureaucrat influenced a shift to early and frequent administration of numerous vaccines to infants in an effort to promote health from cradle to grave [22], and about how a report by Dr. Andrew Wakefield that linked the MMR with autism through gut toxicity became grossly distorted and led to a general distaste for vaccines in the mind of the public. I myself was asked (unofficially) by NIH personnel to investigate the presence of measles virus in Peyer’s Patch samples in gut from autistic and control patients, but I never liked the story and did not do the work, and so have remained on the sidelines of this unfolding tragedy for nearly 20 years.

Dr. Offitt then wrote a second book, “Deadly Choices: how the anti-vaccine movement threatens us all” [23] to deal with this problem. Here, Dr. Offitt points out that the risks of not giving the vaccines for their intended purposes is worse for the individual than taking them and subjecting the infant to the possibility of autism, and infinitely worse for the general public due to the possibility that a sufficient number of unvaccinated children can easily start an epidemic of e.g. measles, as happened in England when groups of parents rebelled against the MMR [23]. In the remainder of this concluding paragraph, I will detail my views on the subject of vaccination. Not everyone will agree with them.

1. One must never forget that ours is a world of risk, and each of us is a survivor. Measles is still the number two cause of morbidity and mortality among children in Africa, second only to malaria, and can easily again become a blight in the West if vaccinations are ignored. Pertussis would also be unwelcome if it returned in force.

2. The true underlying cause of autism is the ubiquitous commensal virus Human Herpesvirus 6 (HHV-6). I was in one of 5 groups which developed this data, but it appears to have vanished from the public and academic eye. Some, but probably not all vaccines and environmental agents act to create ASD by "riling up" HHV-6 which is present lifelong in oligodendrocytes in the brains of everybody, and is thus in a position to do the damage that defines autism. Research on which vaccines "rile up" HHV-6, and which do not, is sorely lacking.

3. The MMR is a highly effective vaccine, but it is also dangerous. It contains three attenuated viruses, measles, mumps and rubella, each of which can infect brain cells and can cause some neurological damage. Measles virus is especially dangerous, because it strongly infects all neural cell types and can possibly cause autism by itself, even without "riling up" HHV-6.

4. Except for the MMR, the fears of the CDC are probably misplaced, since HHV-6 is not a vaccine virus. Therefore, it makes sense to delay the administration of the MMR vaccine until the child reaches the age of 3, beyond the age at which neurological damage can cause ASD, even at the risk of starting a measles epidemic. This topic deserves serious discussion and clinical trials.

Acknowledgement

I note that this article was sponsored by the Weston A. Price Foundation; an organization that I believe has the best interests of the American Public at heart. I do not agree with the Foundation’s call for Congress to remove oversight of vaccines from the Department of Health and Human Services, however. Some government oversight will always be necessary, and DHHS is a good as any other agency, once they are educated as to the correct facts and approaches as outlined in this article.

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