Epidemiologic Studies of MMR Vaccine and Autism

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Outline of presentation

- Epidemiology of
  - autism
  - inflammatory bowel disease
- Wakefield study
  - MMR vaccine, autism, and bowel disease
- Studies regarding MMR and autism
- Studies regarding MMR and bowel disease
- Summary and conclusions
Disclaimer

GW authors are not experts in the substantive areas covered, but assessed the totality of the available epidemiologic evidence
– comments and suggestions gratefully accepted!

Although commissioned by the IOM, the conclusions in this paper are not binding on the IOM
– other factors might enter into causality assessment
– other factors might enter into conclusions and recommendations
Epidemiology of autism

- Pervasive developmental disorders (PPD)
  - Rett’s disorder
  - childhood disintegrative disorder
  - autistic spectrum disorder (ASD)
    » Asperger’s disorder (ASP)
    » autism (usually no period of “unequivocally normal development”)
  » PPD not otherwise specified (PPD-NOS)
    - childhood disintegrative disorder (CDD)
    - atypical autism (later age of onset, atypical or subthreshold symptom)
Epidemiology of autism

- Prevalence of autism (per 10,000) (Fombonne)
  - Median: 5.2; Range: 0.7 to 31.0

- Trends
  - Gillberg and Wing: 3.8% increase per calendar year
  - Kaye et al.: 8 to 29 in 2-5 year old boys between 1988 and 1993 in UK
  - CA Dept. of Developmental Services: 15.0 may reflect increased awareness of availability of services

- Etiology: not much known
Epidemiology of bowel disease

- Inflammatory bowel disease (IBD)
  - Crohn’s disease (CD)
  - ulcerative colitis (UC)

- Incidence of IBD (per 100,000 person years)
  - CD: 0.08 to 7.0
  - UC: 0.5 to 12.8
  - higher in northern areas including UK
  - increasing in other countries to UK levels
  - compare with caution due to varying diagnostic criteria and access to medical care
Epidemiology of bowel disease

Etiology generally unknown, but
- family history is important
- higher in urban than rural populations
- smoking increases risk
  » especially for women
  » children exposed to passive smoking
- other suggested factors
  » oral contraceptives, paramyxovirus, stress
  » inefficient immune system response
  » dietary habits, breast feeding (decreased risk)
The Wakefield study

◆ Case series of 12 children
  – referred to pediatric gastroenterology department with intestinal symptoms
  – with history of PDD with loss of acquired skills
◆ 11/12 found to have non-specific colitis
  – not CD or UC
◆ PPD diagnoses
  – 8 with “definitive diagnosis of autism”
  – 1 “questionable and possible disintegrative disorder”
  – 1 “autistic spectrum disorder”
  – 2 “post-vaccinial encephalitis?”
    » neither term nor ? discussed in paper
The Wakefield study

- Urinary methylmalonic acid excretion significantly elevated compared to controls
  - age-matched and from same site, but selection not described
- MMR was the “exposure identified by parents or a doctor” in 6/8 cases with definitive autism
  - other 2 did receive MMR, but not identified as the “primary exposure”
  - MMR also identified for 1 with questionable autism
  - MMR identified in 1/2 with “post-vaccinial encephalitis?”
The Wakefield study

- No reported detection of measles virus RNA in intestinal tissue or otherwise
- Measles virus RNA was detected in peripheral blood mononuclear cells using RT-PCR/nested PCR from a subset (?) of the 12 autistic enterocolitis patients (3/9)
  - Kawashima (2000)
- Unknown significance of measles virus detection without comparable non-affected pediatric control group
  - control group not clearly described in paper
The Wakefield study

- Authors conclude that they have “identified a chronic enterocolitis in children that may be related to neuropsychiatric dysfunction”
  - typically follows a period of apparent normal development after which children lose skills
  - “in most cases, onset of symptoms was after” MMR vaccination

- The study “did not prove an association” between MMR and the syndrome described
The Wakefield study

◆ Association in epidemiologic studies
  – compare individuals with and without a certain exposure (MMR) to see if the outcome (autism) is higher in the exposed group
  – compare cases (individuals with the outcome) to controls without the outcome to see if cases are more likely to have been exposed

◆ “Association” in this study reflects opinions of patents and physicians, not statistical association
  – difficult to assess unless proximate in time
  – might be better to call this “attribution”
The epidemiologic challenge

Gathering epidemiologic evidence to support or refute Wakefield’s hypothesis presents a serious challenge

- the outcomes in question
  » rare
  » prevalence and diagnostic criteria vary
  » may not have sharp onset or be diagnosed promptly
  » etiologic factors are not well known
- the exposure (MMR) is common
Studies of MMR and autism

◆ Case-control studies
  – UK: Miller et al. (1997)

◆ Case series
  – Finland: Peltola et al. (1998); Patja et al. (2000)
  – North East Thames (UK): Taylor et al. (1999)

◆ Ecological studies
  – UK: Kaye et al. (2001)
Based on National Childhood Encephalopathy Study (NCES), 1976-1979

770 cases of acute encephalopathy in “previously apparently neurologically normal” children
- 16 had received measles vaccine 7 to 14 days prior
- similar proportion in controls (RR 1.85; 95% CI 0.9 - 3.7)

10-year follow-up of 594 (77%) cases
- including 11/16 with measles vaccine
- 3/11 died or had neurological, educational, or behavioral dysfunction
- similar proportion in controls (RR 0.84; 95% CI 0.2, 3.5)
Finland: Peltola et al.; Patja et al.

- Population-based passive surveillance data following nationwide MMR program
  - Judgment of whether outcomes were causally related to MMR based on available clinical information and serum samples
  - 437 adverse events reported in 14 years (0 autism)
  - 31 cases of gastrointestinal symptoms
    » 5 febrile seizures, 2 headaches, 1 ataxia
  - 173 serious adverse events (in 169 people)
    » Factors other than MMR account for up to 45%
NE Thames (UK): Taylor et al.

- Children with autistic disorders
  - born between 1979 and 1992; identified in 1998 from computerized specialized needs/disability registries

- Information extracted on
  - age at diagnosis
  - age at first parental concern
  - age at which regression first became obvious

- Diagnoses confirmed by checking available records
  - 82% of autism cases
  - 31% of atypical autism cases
  - 38% of Asperger’s syndrome cases
Time series analysis to fit exponential trend to number of cases with core or atypical autism
– no evidence of a “step up” after 1987, when MMR vaccine was introduced in the UK

Mean age at diagnosis not statistically different among children who
– received MMR before 18 months
– never received MMR
– received MMR after 18 months
Timing of diagnosis, first parental concern, and regression in children who received MMR

- Clustering of parental concern within 6 months of diagnosis (RI 1.48; 95% CI 1.04 - 2.12) attributed to
  - peak in recorded concern at 18 months (rounding?)
  - peak in MMR vaccination at 13 months

- No other statistically significant clustering

New (unpublished) study with longer induction interval still finds no effect
UK: Kaye et al.

- Time trend analysis based on UK general practice research database (GPRD)
- 305 cases of autism < 12 years of age diagnosed between 1988 and 1999
  - analysis restricted to boys born before 1994 with first diagnosis between 2 and 5 years of age
  - 96% had received MMR
- Annual incidence of autism increased from 0.3 to 2.1 per 10,000 between 1988 and 1993
- 4-year risk of autism increased four-fold between 1988 and 1993, while prevalence of MMR remained constant
Sweden: Gilberg and Heijbel

- **Children diagnosed between 1975 and 1984**
  - 55 with autism by DSM-III-R criteria
  - 19 with autistic-like condition (atypical autism)
- **Birth cohorts defined relative to introduction of MMR**
  - 47 cases (34 autism, 13 atypical autism) born before July 1, 1980
  - 27 cases (21 autism, 6 atypical autism) born after July 1, 1980
- **Since numbers in second period are much less than expected, the date does not support association between MMR and autism**
Summary: MMR and autism

- Focus of Miller study was on measles vaccine
- Most studies not focused on atypical autism or regression
- Analysis limited by
  - trends in diagnosis of developmental disorders and possible background changes in prevalence
  - difficulty of finding a time connection between vaccination and onset of autism
- Limited evidence about the Wakefield hypothesis
Studies of MMR and bowel disease

- **Cohort studies**
  - UK: Montgomery et al. (1999)
  - Olmstead County, MN: Pardi et al. (2000)
  - UK: Morris et al. (2000)
  - UK: Thompson et al. (1996)

- **Case-control studies**
  - East Dorset, UK: Feeny et al. (1997)
  - CA, OR, WA: Davis et al. (2001)
Based on the 1970 British Cohort Study
  - 7019 individuals born in April 1970 and followed through age 26
37 individuals with IBD (17 UC, 20 CD)
  - all but one diagnosed at age 16 or older
Measles infection < 2 years associated with UC but not significant (OR 3.7; 95% CI 0.97 - 13.8)
Measles and mumps infection in same year associated with
  - UC (OR 7.5; 95% CI 2.4 - 23.0)
  - CD (OR 4.3; 95% CI 1.2 - 14.5)
Olmstead County, MN: Pardi et al.

- Eligible cohort: children seen for measles < age 5 at the Mayo or Olmstead County medical centers from 1950 through 1966
  - follow-up questionnaire or telephone survey (57% complete)
  - Standardized incidence rates based on Olmstead County
- Association between early measles infection and IBD
  - IBD and measles < 2 years (SIR 4.4; 95% CI 1.1 - 8.7)
  - IBD and measles > 2 years (SIR 1.9; 95% CI 0.5 - 4.9)
UK: Morris et al.

- Based on the 1970 British Cohort Study
  - 7616 individuals born in April 1970 followed through age 26
  - measles vaccination history at age 5 based on home parental survey

- No association found between measles vaccination by age 5 and later diagnosis with
  - UC (OR 0.57; 95% CI 0.2, 1.6)
  - CD (OR 0.67; 95% CI 0.3, 1.6)
UK: Thompson et al.

- Study of children in 1964 measles vaccine trial
  - annual mailed follow-up surveys through 1994 (n=3967)
  - compared to 1958 birth cohort (NCDS)

- Increase in vaccinated individuals
  - UC (RR 2.05; p = 0.21)
  - CD (RR 2.95; p = 0.01)

- No significant difference in age at vaccination for UC or CD cases compared to all individuals vaccinated
East Dorset, UK: Feeny et al.

- 140 cases in individuals born in East Dorset between 1968 and 1991 with definite diagnosis of IBD
  - two controls randomly selected from same GP, matched on gender and year of birth
  - vaccination history through age 5 obtained from GP records

- No association between measles vaccination and
  - IBD (OR 0.97; 95% CI 0.6 - 1.5)
  - UC (OR 0.84; 95% CI 0.4 - 1.6)
  - CD (OR 1.08; 95% CI 0.6 - 1.8)
CA, OR, WA: Davis et al.

- Vaccine Safety Datalink study in children enrolled in HMOs from 6 months of age or younger between 1958 and 1989
- 142 cases diagnosed as definite, probably, possible, or questionable IBD (75 CD and 67 UC)
  - up to 5 controls matched by HMO, gender, birth year
  - MMR exposure based on medical review of lifetime vaccination history
- No statistically significant association between MMR and IBD
Viral detection

  - using electron microscopy, in situ hybridization, or monoclonal antibody to measles virus

- Haga (1996), Afzal (1998), and Chadwick (1998) find no detectable measles virus in intestinal tissue and peripheral blood mononuclear cells
  - using RT-PCR/nested PCR techniques
  - adults (ages 17-65) with UC, CD, and indeterminate colitis

- No individuals diagnosed with autism and enterocolitis are included in these studies
Limited evidence of an association between measles vaccine or infection and IBD
- Measles vaccine or measles infection, not MMR
- IBD (UC and CD), not non-specific colitis

Analysis limited by
- accuracy of retrospective diagnoses
- differing definitions of IBD

Almost no evidence about the Wakefield hypothesis
Conclusions

◆ Wakefield hypothesis
  – focused on 3-way relationship among MMR, atypical autism with regression, and non-specific colitis
  – based on “attribution” of cause by physicians and parents

◆ Other epidemiologic studies
  – focused on 2-way relationship between MMR and PDD or IBD
  – different outcomes and sometimes different exposures
  – difficulties of studying rare outcomes

◆ Epidemiological evidence reviewed here is inadequate to accept or reject a causal relationship between MMR and autism
MMR and autism evidence model

MMR
- Measles vaccine
- Measles infection

- Atypical autism w/ regression (CDD?)
- Non-specific colitis

PDD
- Autism

IBD
- CD, UC

Strength of evidence

Evidence favors rejection
Evidence is inadequate
No evidence

Evidence favors acceptance
Evidence establishes

RR
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