Horizontal transmission and measles vaccine: implications for neo-pathogenesis, measles control, and measles eradication

Andrew J Wakefield MB.BS., FRCS., FRCPath,
Executive Director
Thoughtful House Center for Children
Austin, Texas 78746
andy.w@thoughtfulhouse.org

Patrick Tierney
Department of Latin American Studies
University of Pittsburgh
ptrcktiem@msn.com

Stephen Walker Ph.D.
Assistant Professor
Department of Physiology and Pharmacology,
Wake Forest University School of Medicine.
Winston-Salem NC 27101
swalker@wfubmc.edu

John Lednicky Ph.D.
Midwest Research Institute
425 Volker Blvd
Kansas City, MO 64110-2299
jlednicky@mriresearch.org
Arthur Krigsman M.D.
Associate Professor, New York University Medical School
Clinical Director, thoughtful House center for Children,
Austin, Texas, 78746
arthur.k@thoughtfulhouse.org

Paul Ashwood Ph.D.
Assistant Professor
Department of Medical Microbiology and Immunology and the M.I.N.D.
Institute, 2805 Wet Lab Building,
50th Street, Sacramento, CA 95817
pashwood@ucdavis.edu

Correspondence to:
Dr Andrew J Wakefield MB.BS., FRCS., FRCPath.
3001 Bee Caves Road, Suite 120
Austin, Texas, 78746
Tel: 512 732 8400
Fax No: 512 732 8353
www.thoughtfulhouse.org
info@thoughtfulhouse.org
Abstract
This review addresses the possibility of horizontal transmission of measles vaccine virus in the context of evidence from recent molecular epidemiology and the emergence of apparently novel, overlapping pathologic syndromes in non-human primates and children. The review presents the evidence that age of MMR vaccine exposure is associated with an increased risk of autistic spectrum disorder. The syndrome of autistic enterocolitis is described and its emergence in siblings of vaccinated children with this disorder, where these siblings are unvaccinated and yet harbor measles vaccine-strain virus in their intestinal lymphoid tissues, is presented as direct evidence of horizontal transmission and its likely pathologic consequence. The implications of these factors for the interpretation of current epidemiology, measles virus surveillance, and global measles control and eradication, are discussed.

Introduction: measles virus vaccine and horizontal transmission
Measles virus vaccine is a live viral vaccine. All vaccines in widespread use derive from the Edmonston virus first isolated by Enders and Peebles in 1954. The passage history of this vaccine is shown in Figure 1.
Figure 1. Passage history of the Edmonston virus. Temperature of passages assumed to be at 37°C unless otherwise stated. HK, human kidney; HA, human amnion; CE(am), intra-amniotic cavity of chick embryo; CEF, chick embryo fibroblast; DK, dog kidney; WI-38, human diploid cells; SK, sheep kidney (Adapted from 1).

The vaccine virus replicates within the host eliciting an immune response that protects, to a variable degree, against subsequent exposure. The potential for transmission from vaccinated to non-immune individuals is, therefore, an important theoretical concern. Horizontal transmission refers to spread between individuals unrelated as mother to child. Vertical transmission refers to spread from mother to child, for example, in utero, intra partum or through breast-feeding.

Millson first reported a possible case of brother-to-sister transmission of measles after measles-mumps-rubella (MMR) immunization in 1989 (2). A 4-
year old boy had onset of clinical measles with Koplick spots 10 days after MMR vaccination. His 8-month old sister developed an almost identical clinical picture 2 days later. Both children followed an identical course with complete recovery. No laboratory tests were undertaken to confirm measles infection. Campbell responded on behalf of the Joint Committee on Vaccination and Immunization (JCVI), stating that ‘extensive testing and experience with measles vaccine and MMR vaccine had not shown evidence of vaccine virus transmission to susceptible contacts’ (3). This ‘evidence’ was neither provided nor cited. He concluded that ‘there is no risk of virus transmission following measles, mumps, or rubella vaccine’. This conclusion was premature and the case is simply made. For example, following maternal vaccination, rubella vaccine virus transmission from mother to infant in infected breast milk has been established and is declared as a warning in the MMR product insert. Horizontal transmission of mumps vaccine virus from a vaccinated to a susceptible sibling, with molecular confirmation, has been reported (4). The likely vertical transmission of measles vaccine through breast feeding is described by Yazbak and Diodati (5).

A critical review of early measles vaccine transmission studies

The foregoing opinion, expressed so resolutely by Campbell of the JCVI, is the public face worn on the question of transmissibility by vaccine policy makers. The evidence upon which this perception relies merits scrutiny, given the importance of this issue for public health. The original studies of measles vaccine were relatively small, poorly controlled, of short follow up and methodologically limited. The reporting itself is somewhat ambiguous and the findings, as described, are inconsistent with some of the overly dogmatic conclusions. This is exemplified by a series of papers from Katz (one of the architects of measles vaccine experimentation and policy) and his colleagues,
including one based upon a 1960 study of 39 children (6). Despite the claim that there was no evidence of horizontal transmission, the authors state ‘The earliest exposure in an immunized child to a sibling contact was nine days after vaccination and only three days after fever developed…In this case the unvaccinated child in whom measles developed had a known outside exposure and ran a typical moderately severe course of measles, making it unlikely that this was acquired from the vaccinated child.’ No details of either the ‘contact’ or the evolution of measles in the unvaccinated sibling are provided, while measles had developed in a susceptible contact exposed to a vaccinee 9-days after inoculation i.e. ‘who gave what to whom?’, is uncertain. The author’s uncritical view and unsubstantiated exoneration of the vaccine, is a feature that appears to pervade these early reports. Elsewhere, Smith et al describe their observations on siblings of vaccinees receiving the Goffe (Edmonston-derived) strain of the vaccine in the UK (7). Unvaccinated siblings developed ‘an unusually high prevalence of upper respiratory symptoms seven to ten days after [sibling] vaccination’. Despite the consistent pattern of these symptoms occurring at a relatively discrete time point after sibling vaccination with live measles virus, the authors suggested that the symptoms ‘might possibly be due to intercurrent infection in the family and ‘not necessarily to the vaccination’. This statement nonetheless, clearly acknowledges the possibility of horizontal transmission.

In summarizing the US studies, Katz and colleagues (8) reported that two other investigating groups (6,9) ‘both commented upon the concomitant prevalence of cough and coryza [typical features of measles] among unvaccinated controls’. The authors later note that Lepow et al (9) and Haggerty et al (6) followed a total of 21 successfully vaccinated children who had ‘no evidence of disease when intimately exposed in their homes a few weeks or months thereafter to siblings with natural measles’. The possibility of a reverse causation – transmission from vaccinated to
susceptible sibling in the ‘few weeks or months’ following vaccination does not appear to have been considered. As lead investigator in an experimental study of measles vaccine in institutionalized children with mental deficiency (10) Katz noted ‘absence of clinical signs of infection in susceptible contact controls and inability to demonstrate inapparent infection of controls by alteration of serologic tests’. He concluded, ‘Accordingly, there seems to be little or no chance that attenuated measles virus would regain virulence as a result of repeated passages from one human being to another’. Katz based this conclusion on observations in a total of 2 susceptible ‘controls’.

None of the aforementioned findings provide direct evidence of horizontal transmission. Nonetheless, a different complexion might be placed upon the findings of these studies in a more objective search for evidence of possible horizontal transmission. Certainly, the lack of laboratory evidence for transmission, limited by methodology and numbers, could not exclude its occurrence. Since the availability of PCR, the potential for shedding of measles vaccine virus in urine (11,12), nasopahrangeal aspirates, and nose and throat swabs (11), for in excess of 3 weeks post-vaccination in some instances (13), has become apparent.

**Horizontal transmission of measles vaccine virus**

As with rubella vaccine, the position on measles vaccine virus transmission has shifted significantly. A review by Pütz *et al* draws attention to the implications for the increasingly persuasive evidence of measles outbreaks originating in vaccinated individuals, in limiting efforts towards global measles eradication (14). These outbreaks consist of clade A virus infection (Figure 2a) occurring in an atypical pattern. Clade A virus outbreaks, unlike those of wild-measles,
occur sporadically, are not geographically confined, and show virtually no genetic diversity over time. In the laboratory, clade A viruses behave like the vaccine virus and unlike most wild-type viruses in that they grow spontaneously in Vero cells.

**Unraveling the origins of clade A measles virus**

Nucleotide sequence analysis of the different genes of measles virus has shown that most variation occurs in the hemagglutinin (HA) and carboxy-(C) terminal region of the nucleocapsid protein (NP). Sequence analysis of these two viral genes from different viruses has provided a classification in which isolates are separated into eight clades (A-H), each containing variations or genotypes (15). This molecular epidemiology approach has enabled decoding of the genetic signatures and hence, the origin of the respective clades. Clade A viruses, which are virtually identical to the measles vaccine strain, bear vaccine strain signature single nucleotide polymorphisms. In particular, the genetic consistency between clade A isolates and derivatives of the progenitor Edmonston vaccine virus occur in the HA (Figure 2b) and the C-terminal region NP genes. The history of this discovery merits description in some detail if one is to appreciate the significance of the findings.
Figure 2a. Phylogram of representatives of the 15 measles virus genome types identified at present (5) along with 4 strains retrieved from sequence databases and found not to fit into the 15 genome types of WHO (5) (Clade A highlighted). All bootstrap values above 80% for major clusters are indicated (Adapted from 16).
Figure 2b. Phylogram of the 30 sequences of the HA-coding region retrieved from the sequence databases showing the highest similarity to the HA sequence of the Edmonston strain. All bootstrap values above 80% are indicated (Adapted from 16).
Some of the sentinel data emerged from a measles outbreak in Coventry in mid-1993. Outlaw and Pringle described the characterization of 5 clinical measles isolates, 2 of which came from children vaccinated with MMR, 2 cases were unvaccinated and one case, a Chinese student, was of unknown vaccination status (17). There was no obvious link or contact between the cases. Their findings were summarized as follows: “Comparisons were made with the Edmonston strain and the current MMR vaccine strain. It was found that a high degree of homology existed between all strains examined, but that the majority of clinical samples shared a premature termination signal – A to T substitution at nucleotide position 9019 - that potentially shortened the haemagglutinin (HA) protein by 35 amino acids”. None of the changes found in the Coventry isolates matched any other isolate from the UK or US. NP and Matrix (M) gene regions resembled vaccine strain virus more than either of the two wild-type lineages circulating at that time in the UK.

A 2002 Danish study reported on the characterization of 18 measles virus strains isolated from a serum archive that antedated the institution of mass vaccination in Denmark in 1987 (18). The considerable genetic diversity exhibited by these wild isolates was ‘at odds’ with the prior assumption that one genome type prevailed among globally circulating measles virus. Their data indicated that, in contrast with the genetic diversity of wild-type isolates, the similarity of vaccine strains could be attributed to their having derived from the same primary (Edmonston) isolate compared with the relatively disparate ancestry of wild-type viruses.

Specifically, vaccine strains and isolates of apparent vaccine ancestry all shared four signature polymorphisms in the HA coding region, C72, T129, C826 and
A1149, none of which were present in the contemporaneously circulating non-clade A strains. Elsewhere, a unique mutation introduced to the Edmonston-Zagreb measles vaccine strain – A1451 – was also found in clinical isolates including Leningrad-16, Changheun-47 and Changai-191 (19) and “in the Asian type A field strains”, thus, as Christensen and colleagues suggest, “supporting the hypothesis that Zagreb in the former Yugoslavia could have played a geopolitical role in disseminating the Edmonston strain to Asia” (18). Continued, sporadic re-emergence of ancient clade A genotypes is another possibility.

A further polymorphism - A351- documented exclusively in the Schwarz and Edmonston-P9 vaccine strains, was identified in South African clade A field isolates, where the Schwarz vaccine was used, but has not been recorded in any clade A field isolate from Europe, Asia or the USA (21). Wairagkar et al identified two clade A isolates in 11 measles virus-positive throat swabs obtained from sporadic and outbreak cases in Pune, India during 1996-1998 (20). The NP-gene sequences of these isolates were identical to the Edmonston-Zagreb strain used in India. One HA-gene sequence was identical to the vaccine strain while the other differed by 4 nucleotides out of 1,854. Neither case had any record of having been vaccinated. The authors concede the possibility of these being either vaccine-associated measles or laboratory contamination. Given the distinct HA-gene signatures, the latter explanation seems unlikely. In the vaccine era, clade A measles virus has been detected additionally, in acute cases of measles in South and North America, Japan, Eastern Europe and Finland (22). During a 3-year investigation in Australia, vaccine associated illness accounted for ten sporadic cases of clade A infection, mainly but apparently not exclusively in symptomatic infants that were recently
vaccinated (13). Details of these other potentially important cases were not provided by the authors.

Christenesn and colleagues concluded that “a small number of clinical manifestations of measles virus worldwide from which strains similar to the vaccine strain were identified, were vaccine related rather than being caused by members of a persistently circulating ancient genome type” (18).

Rota and Bellini at the Centers for Disease Control and Prevention (CDC), have contributed considerably to the genetic epidemiology of measles virus. In commenting upon the earlier findings they referred initially, to the Coventry isolates as ‘wild circulating measles virus of Type A’ (22). In reference to the stability of group 1 (clade A) measles virus – then presumed to be ‘wild-type’ - they stated that ‘it is very unlikely that [they] represent laboratory contamination or re-isolation of vaccine virus from recently vaccinated persons’. They were to reverse this opinion, presumably in light of the Danish, Indian, and other data, later describing the formerly ‘wild’ clade A isolates as probable ‘vaccine viruses or laboratory contaminants’ (23). The latter explanation is highly unlikely, given the idiosyncrasies of the sequence data and the pattern of associated outbreaks (17,20).

Transmission of measles vaccine virus is likely to be a real if apparently uncommon occurrence, as least if the frequency of this event is judged by the presentation of typical clinical measles infection in susceptible contacts and the rigor of molecular sleuthing and reporting. However, neo-pathogenesis – the emergence of a new clinical disease or syndrome, arising as a consequence of vaccination and horizontal transmission - would be likely to escape detection for some time. Early efforts to examine transmissibility of measles vaccine virus
were limited in their scope and sensitivity, given the lack of adequately permissive cell lines and molecular detection technology at the time. A critical review of the data indicates the possibility of horizontal transmission even in the limited early trials (6-10). Moreover, study design did not account for (i) the potential for delayed transmission from prolonged virus shedding by immunosuppressed individuals (a factor of increasing concern) and (ii) possible change in the route of transmission following injection rather than respiratory contagion. Both of these factors and the potential for fecal transmission, in particular, are of specific interest to some of those involved in the investigation of children with autistic regression and bowel disease with onset following MMR vaccination, issues that will be considered below.

**Horizontal transmission: evidence from non-human primates**

Measles infects non-human primates, reproducing key aspects of the human disease including fever, rash, systemic lymphoid infection, immunodeficiency, and induction of specific protective cellular and humoral immune responses. Chen and colleagues described sporadic measles-associated colitis in captive Tamarins (*Saguinus mystax*) following a measles outbreak in their colony (24). Similarly, experience involving measles vaccination of captive Rhesus macaques at the UC Davis colony identified a sporadic diarrheal disease with failure to thrive and apparent behavioral disturbances [unpublished data]. Surgical pathology of ileal and colonic tissues revealed an enterocolitis consistent with moderate-to-severe human inflammatory bowel disease (Figure 3). TaqMan RT-PCR analysis of gut tissues for measles virus Fusion (F) gene sequences was positive in these animals (unpublished observations).
In describing experimental measles exposure in this same colony, McChesney later wrote ‘In collaboration with the CDC we have tested several novel measles vaccines in Rhesus monkeys. We have detected persistent measles virus infection by reverse transcriptase polymerase chain reaction (RT-PCR) in the tissues of monkeys exposed to pathogenic measles virus from six months to one year earlier. Tissues that were PCR-positive [for measles virus] included peripheral lymph node, spleen and gut.’ (McChesney M, personal communication) The ability of measles vaccine strains to establish persistent infection of the intestine associated with pathologic change, appears to have been confirmed in these preliminary studies.

Figure 3. Chronic active colitis in a Rhesus macaque, as described above. A dense mononuclear cell and polymorph infiltrate is accompanied by crypt abscess formation and distortion of crypt architecture (Hematoxylin and eosin; original magnification x40).

Subsequently one of the authors [JL] helped investigate a pattern of disease in one type of monkey at the Brookfield Zoo, Maywood, Illinois. The monkeys
were New World primates, *Callimico goeldii*, some of whom had received measles vaccine prophylaxis. Previously thriving, the population of *C. goeldii* in American zoos has been in decline since the 1990s, with mortality exceeding natality. A retrospective tabulation of mortalities among animals > 1 year old showed renal involvement. Nevertheless, a pattern of presentation, with chronic diarrhea, failure to thrive and apparent, if somewhat poorly characterized behavioral disturbances, was evident. This is of interest, given reports of the propensity of New World primates to intestinal complications following measles, with depression, loss of appetite, and high mortality (24). In this unplanned, diagnostic study at Brookfield Zoo, tissues from affected animals were submitted to pathologic and virologic examination. A number of viruses were isolated from various primate tissues including a cytomegalovirus, a retrovirus, and SV40 from kidney cells (25) and a different syncytium-forming virus - not a retrovirus - from other tissues (Figure 4; unpublished). Microscopy of diseased intestinal tissues revealed sporadic giant cell syncytia consistent with viral involvement. The syncytium forming virus appeared to be a paramyxovirus by electron microscopy. This author [JL] suspected *Canine distemper virus* (CDV), as CDV had been causing outbreaks of distemper among area wildlife and had been transmitted to some animals in the zoo (26,27). Like measles virus, CDV is also a morbillivirus. Contrary to popular belief, CDV can infect primates (28) as well as certain omnivores (29). However, immunohistochemistry using an antibody specific for CDV was negative, but weakly positive with a CDV antibody that also cross-reacts with some other morbilliviruses (including measles virus). Using a universal RT-PCR protocol for morbilliviruses followed by sequencing, the virus was identified, to the author’s disappointment, as measles virus, not CDV. Additional RT-PCR work and sequencing identified Moraten measles vaccine-strain specific genomic
sequences. Subsequent molecular tests confirmed the presence of the same measles virus strain in the monkey tissues. It is important to note that the laboratory had not worked with measles virus previously. What was somewhat unexpected in these studies is the fact that non-vaccinated cage mates of vaccinated, diseased *Callimicos* manifested the same tissue pathology and the same virologic findings as their sick, vaccinated cage-mates. Irrespective of any role for measles virus in the intestinal pathology, the data provide direct evidence of horizontal transmission. The implications for enteric spread in the contaminated environment of cage mates with diarrheal disease associated with shedding of a vaccine-derived virus and possible pathogen, are self-evident.

Figure 4. Syncytial cytopathic effect of Moraten-strain measles virus grown from the tissue of *Callimico goeldii* in Vero cells culture at X weeks. Original magnification x100
Horizontal transmission: evidence from the field

The question of whether measles vaccine has become transmissible among so-called “virgin-soil populations” arose in connection with a measles vaccination experiment conducted by the geneticist James Neel, among the Yanomami Indians of Venezuela. In 1968, despite an apparent prohibition by the Venezuelan government, Neel employed the most reactive of the early measles vaccines - the Edmonston B - on the Yanomami (30). The results were unexpected. He recorded the highest temperatures for any measles vaccine among any population (31) Then a measles epidemic, of unknown origin, spread in Neel’s words, “as a wave away from the original point” where the vaccinations had occurred. And, “Within two months of the first case, measles had developed in no fewer than 15 villages” (31). Steinworth-Goetz, a physician and anthropologist, described measles morbidity and mortality among the Yanomami (32): “Many Indians fled deep into the forests, but for most of the people living near the Orinoco it was already too late. They carried the disease germs with them, infecting others and dying by the score. They had absolutely no resistance. Only a very few even developed the characteristic rash, which is a sign of the skin’s fight to throw off the disease. Mucous membranes became horribly inflamed, with extreme toxic vomiting and diarrhea. Many had hemorrhaging of the inner walls of the larynx. Many developed pneumonia and died from it. All too often even relatively mild cases failed to respond to penicillin.”

Although Neel claimed that a Venezuelan doctor, Marcel Roche, had diagnosed measles in an anonymous Brazilian boy on the same day the expedition arrived, mission records (33) and Neel’s own correspondence with Roche contradicted the claim (34). In fact, sound records of the expedition, made by the filmmaker Timothy Asch, showed that measles caught the expedition by surprise. Asch’s audio tapes of the expedition, discovered by one of the authors (PT) and
witnessed by editorial staff at Science, suggest that expedition members themselves, bewildered by the way the disease seemed to be springing up everywhere around them, wondered whether the vaccine might be a cause (35). The film of Neel’s Atomic Energy Commission-sponsored genetics – entitled Yanomama: A Multidisciplinary Study – showed the residents of a village, Patanowa-teri, being vaccinated against measles in order to prevent an outbreak. The humanitarian goal was achieved, according to Neel, the film’s narrator. “This village is fortunate”, he said. “It was vaccinated in time” (36). This has since been refuted by an investigation by the American Anthropological Association: “Of course we know now that measles did reach Patanowa-teri, causing many deaths” (37). An independent investigation by the Venezuelan Congress found that Yanomami survivors blamed the vaccine for the epidemic (38).

Is it likely, or even tenable, that villagers who had lived without epidemic measles exposure but with regular outside contact, should first experience a natural measles epidemic at precisely the same time and apparently, in precisely the same place as it was first exposed to a measles vaccine capable of being shed; furthermore, with the same pattern of subsequent spread as the vaccination procedures.

Further questions about the role of vaccinated individuals in spreading measles have been raised by researchers in the arctic, where, historically, identification of measles carriers has been highly accurate (39).

The Scoresbysund district of Greenland represents an ideal area for the study of measles vaccination; it is an isolated and relatively closed community that has very little contact with the outside world. A measles vaccination program
for its 500 inhabitants, mainly Polar Eskimos, was conducted in 1967. Pedersen et al reported that 94 percent of this population, which had never been exposed to natural measles, was vaccinated using the Schwarz live further-attenuated vaccine (40). Children born after 1967 likewise received measles vaccination. In a subsequent study, Pedersen et al noted that a temporary increase in measles antibodies occurred in the majority of those who were examined 2-4 years after vaccination (41). This was not accompanied by clinically observed measles. Pedersen suggests that this was most likely due to an inapparent measles infection in a population considered highly immune after vaccination (41).

Based upon these observations and in the absence of any identified source or carrier, Pedersen and his colleagues made the controversial suggestion that “…measles can spread from a majority of vaccinated, to a minority of unvaccinated people, causing overt disease” (41).”

**Measles virus and neo-pathogenesis in human disease**

From the foregoing human and non-human primate examples, transmission of measles virus – specifically fecal-oral transmission - may be an important alternative to classical respiratory portal, particularly in the context of measles vaccination and a potential intestinal pathogen. It is of relevance, therefore, that measles virus has been implicated in the cause of a number of chronic human immunopathologies including inflammatory bowel disease (IBD) (42-49). While the evidence is controversial (50-52), there is a body of data indicating that atypical exposures to measles virus – younger age of infection (47,49) and concurrent exposure to mumps virus (48,53,54) - are associated with an increased risk of IBD. These findings are consistent with the knowledge that early measles virus exposure is a major risk for acute and delayed adverse
outcomes, including persistent infection and chronic immunopathology, and
that ‘interference’ associated with concurrent viral exposures alters the antiviral
immune response (Reviewed by Wakefield and Montgomery, 54). Until
recently, however, persistent measles virus infection in intestinal tissues from
IBD patients had not been confirmed by RT-PCR based methods, a key factor
in any argument for persistence and the potential for enteric transmission.

In seeking to resolve the latter issue, one of the authors (AW) initiated a study
by Drs Ward and Seidman, working respectively at McGill University and St
Justine Children’s Hospital in Montreal, encouraging them to conduct RT-PCR
analysis of intestinal tissues taken from children with IBD and controls. The
rationale was that, if measles were associated with onset of IBD, it would more
likely be detected in children whose affected tissues were biopsied in closer
temporal proximity to their vaccine exposure, compared with adults presenting
20-30 years after measles or measles vaccination.

Ward subsequently presented the results of this study, describing the detection
of measles virus NP gene sequences in 43% of IBD cases and 17% of non-
IBD controls, (Ward BJ, MacFarlane S, Vinh D, Wild G, Seidman E.
Microbiol. Reference not available). Of added interest was the identification of
an apparently novel paramyxovirus NP gene sequence in one case. In addition
to presenting his findings to the American Society for Microbiology, Ward
communicated his findings to the Oak Brook meeting on autism and
vaccination, convened by the American Academy of Pediatrics (56) and was
apparently encouraged to publish them in full by the organizing committee. He
has declined to publish the data on the basis that, ‘the differences between cases and
controls did not achieve statistical significance'. Ward’s reasoning was also confirmed on a separate occasion by his co-worker Dr Seidman (personal communication to Professor John Walker-Smith, then at the Royal Free Hospital School of Medicine).

The fact that the statistical difference in a relatively small sample achieved a p value of 0.07 is relatively trivial in comparison with the potential biologic significance of establishing, for the first time and in the face of prevailing dogma, persistence of vaccine strain virus in diseased and control intestinal tissues.

The data, while in the public domain, remain unpublished as a full scientific paper. This notwithstanding, preliminary data from the analysis of pediatric bowel tissues indicate the potential for persistent measles virus infection following vaccination, consistent with McChesney’s findings in the Davis macaques.

**Neo-pathogenesis: autistic enterocolitis and MMR vaccine**

Autism spectrum disorders (ASDs) are a complex set of developmental disorders of childhood, characterized by pervasive impairments in social interaction; deficits in verbal and non-verbal communication and stereotyped, repetitive patterns of behavior and interests. Manifestations frequently begin within the first three years of life. The prevalence of ASD diagnoses has increased substantially over the last several decades in developed countries (57,58). The etiologic origins of this epidemic are not known but must involve a major environmental contribution.
Recognition of a viral etiology in autism is not new. Indirect clues come from the observation of factors such as a season-of-birth effect in different countries (59-63). This phenomenon appears to have disappeared from more recent birth cohorts (64), a trend that may reflect an historical pattern of epidemic infectious exposure that has changed in more recent years.

Atypical patterns of exposure to measles, mumps, and rubella viruses, in their natural form, have been linked to childhood developmental disorders, including autism (65,66) and disintegrative disorder (67). Measles-containing vaccines have been causally linked to developmental regression (68).

Ring et al modeled the number of autism births with epidemics of measles, rubella, poliomyelitis, viral meningitis and viral encephalitis. Children born during epidemics of measles and viral meningitis were at significantly greater risk of developing autism (66). While measles may have accounted for a relatively modest number of cases in this historically rare condition, transition to a high risk pattern of exposure may have changed this.

A possible association between MMR vaccination and autistic regression in previously developmentally normal children has recently been reported (69,70). The evidence for this link is controversial, reflecting the widely differing conclusions of basic and clinical science versus epidemiology. The background to this phenomenon merits description if one is to appreciate the possible implications for neo-pathogenesis and horizontal transmission.

**Age of exposure** As documented earlier, younger age of exposure to measles virus is associated with an increased risk of adverse outcome, including persistent
infection and delayed disease. Is there evidence for such a risk in autism? A recent epidemiologic study by Richler et al posed the question of whether there is an autism phenotype characterized by regression associated with significant GI symptoms (one or more symptoms lasting for more than 3 consecutive months) following MMR vaccine in a previously developmentally normal or near-normal child (71). Children meeting these criteria were compared with all other autistic children in their study cohort. In this, the only epidemiologic study to at least attempt to segregate this sentinel autism phenotype, age-of-exposure to MMR vaccine was significantly lower (mean age 14.38 months) when compared with the remaining autistic population (mean age 17.71 months; p<0.05). By limiting their ‘regression’ group to those children who had a skill at 24 months that was subsequently lost, thus excluding all children who regressed between 12 and 24 months (the majority of the relevant population), the true extent of the age-of-MMR-exposure phenomenon will potentially have been masked. Strangely - and at odds with their own reported findings - the authors concluded that, ‘there was no evidence that onset of autistic symptoms or of regression was related to MMR vaccination’.

Three further aspects of age-of-exposure to MMR and autism have been reported: DeStefano and colleagues performed a case-control study comparing age at first MMR vaccination in children from the Atlanta metro area (72). By 36 months of age, significantly more cases with autism (93%) had received MMR than controls (91%)(Odds Ratio 1.49; 95% confidence interval [CI] 1.04-2.14). This association was strongest in the 3 to 5-year age group with an Odds Ratio of 2.34. Due to diagnostic delay, a significant proportion of this group had yet to be diagnosed with autism, potentially underestimating this risk. Moreover, in a subgroup analysis looking at children with different disease characteristics, they found a significant association between MMR vaccination by 36 months and autistic
children with no evidence of mental retardation (IQ>70; OR 2.54 [1.20-5.00]).
The odds ratios were increased to 3.55 in a subgroup analysis adjusted for birth
weight, multiple gestation, maternal age and maternal education, thus
strengthening the association between age-of-exposure to MMR and autism. It is
interesting that their ‘regressive group’ did not show this effect although the
interpretation of this finding is severely constrained by their retrospective
ascertainment of regression from medical records. First, regression did not form
part of the diagnostic algorithm for autism and second, the concept of regression
conflicted, until very recently, with the beliefs of most autism diagnosticians. IQ,
on the other hand, is an objective measure and a normal IQ appears to be an
increasingly common feature among recent cohorts of affected children (73). An
IQ within the normal range may well reflect a period of normal cerebral
development and in this instance, be a better marker of the late-onset phenotype
than retrospective record review. Having tested a hypothesis and found a
significant association between autism and age of first MMR exposure, the
authors, somewhat curiously, ascribe this effect to an ‘artifact of immunization
requirements for pre-school special education attendance in case children’. Such an
interpretation would only possibly be valid if the immunization mandate for
normal pre-school children were different from that of special education children;
it is not. Moreover, the special education group, with a likely excess of
contraindications to MMR vaccination such as seizures, should have a lesser
exposure to MMR. In addition, if there were no true association, lower exposure in
the special education group would be expected in light of higher levels of parental
concern and consequent rates of abstention in this group, a possibility that could
have been easily checked by comparing the proportions of exemption filings held
by law in all state schools. This notwithstanding, the data of DeStefano et al are
not consistent with the author’s post hoc rationalization.
Second, Edwardes and Baltzan (74) reanalyzed the California autism data of Dales and colleagues (75) who had reported that there was "essentially no correlation" between rates of autism and measles-mumps-rubella (MMR) vaccine uptake. Nonetheless their data showed that the age of immunization was becoming younger between 1981 and 1993 (a factor of potential relevance to DeStefano et al's observations of a statistically more significant association between autism and earlier MMR vaccination in more recent birth cohorts (72)). Edwardes and Baltzan plotted the ratio of children immunized before age 17 months with those immunized between age 17 and 24 months. This ratio increased 200% from 1981 to 1993. The data suggest that the rate of early MMR immunization is correlated with the incidence of autism. Dales and colleagues acknowledged in their response that, "these data do indicate a temporal trend toward MMR vaccine receipt at younger ages" but pointed out the disproportionately low magnitude of rise in MMR vaccine coverage of young children compared with the approximately 400% relative increase in the incidence of autism (76). The latter argument, which appears to imply the assumption of some simple mathematical relationship between age and risk, may not be appropriate and is less important than the potential impact of a shift, at the population level, towards a possible high-risk pattern of exposure, that is, younger age. Such a risk, normally distributed by age, could account for a substantial and apparently disproportionate increase in cases with progressively earlier MMR exposure.

In addition, what these authors also failed to take into account is the potential impact of booster MMR vaccination that, according to recent data on re-challenge with MMR (77), might lead to a substantial impact on the disease and thus, the numbers of children meeting full syndrome autism (as a requirement for registration in the California Developmental Disorders System, 73).
Third, Suissa pointed out that according to the Danish data of Madsen et al. the rates of autistic disorder by age at MMR vaccination, are 18.9, 14.8, 24.6, and 26.9 per 10^5 per year respectively for ages <15, 15-19, 20-24, 25-35, falling to 12.0 per 10^5 with age at vaccination >35 months, compared with the overall rate of 11.0 for the reference group of no vaccination, over all ages (78,79). Suissa considered it somewhat implausible for the age-adjusted rate ratio to fall below 1 (as presented), unless the risk profile by age in the unvaccinated is vastly different than in the vaccinated. Thus, rather than an apparent association between exposure and outcome being a spurious result of confounding, this would actually represent effect modification. The data support the hypothesis of an association between exposure and outcome, modified, rather than confounded by, age of exposure.

While an effect of age of exposure to MMR vaccine on autism risk is evident from these studies, the nature of that risk is not known.

**Evidence of viral pathogenesis** In considering the potential role of measles virus, an enterotropic virus capable of producing profound immune disruption, in the etiology of a regressive autistic encephalopathy, it is evident that affected children have a high frequency of GI symptoms (80,81). Investigation of these symptoms has provided substantial reproducible evidence for GI and immune system pathology (82-90). Such findings may have important implications for mode of horizontal measles virus transmission.

Briefly, the mucosal lesion consists of a patchy, mild to moderate pan-enteric inflammation with lymphoid nodular hyperplasia and is consistent with a viral etiology. Within the mucosa there is an increased CD3^+ and CD8^+ T-cell density, IgG and complement C1q co-localization at the epithelial basolateral membrane,
suggestive of autoimmunity. This is accompanied by marked pan-enteric immune dysregulation with excess CD3″TNF-α, CD3″INF-γ, and Th2 cytokines, and a reduced counter-regulatory IL-10 (91,92). These changes are largely mirrored in the spontaneous peripheral blood CD3″ lymphocyte cytokine profile of affected children, and in the induced cytokine production by peripheral blood mononuclear cells in response to lipopolysacharride, phytohemagluttinin and dietary antigen exposure (93-95). These changes are frequently accompanied by lymphopenia in both CD4″ and CD8″ populations (87). Consistent with allergic predisposition, IgA is usually in the lower quartile of the normal range (87). Differentiation status of circulating CD8″ lymphocytes indicates an over-representation of the chronically activated/exhausted CD38″CD28CD27″ phenotype (96), consistent with a persistent viral infection (unpublished data).

It is likely that reported physiologic GI dysfunction in many affected children, including impaired brush border enzyme activity (83), dysbiosis (97-99), permeability changes (100,101), oxidative stress (102), and elevation of systemic markers of inflammation (103), are a reflection of this underlying mucosal immunopathology. Moreover, given the ability of inflammatory cytokines to modulate neuronal survival (104) and differentiation (105), as well as dendrite growth and complexity (106), a role for the mucosal immunopathology – possibly as a primary event – in the pathogenesis of neurologic injury and autism is plausible. This scenario is supported by both the experimental data of Welch et al showing that a primary inflammatory bowel disease can lead to immediate-early (Fos) gene activation in the brain in those areas involved in autism (107) and the observation that systemic immune activation can modulate microglial activation status (108). Immunohistochemical evidence of microglial activation in proximity to neuronal loss, has recently been reported in post-mortem autistic brains (109).
The aggregated findings are consistent with a persistent viral pathogenesis, in particular with a virus capable of producing substantial immune disruption. Autistic enterocolitis exhibits a striking overlap with human immunodeficiency virus (HIV) enteropathy, features of which include inflammation and LNH in which the hyperplastic lymphoid follicles are a nidus of HIV infection.

**Viral detection:** In light of clinical histories and pathologic findings, and the recognized enteric (110) and immunologic effects of measles virus (111), viral RNA and protein were sought in the reactive ileal lymphoid follicles.

Analysis of ileal lymphoid tissues from affected children and developmentally normal pediatric controls, was conducted with well characterized specific antibodies against measles virus, including WHO reference monoclonal antibodies, mumps, rubella, HSV I & II, HIV and adenovirus (112). A characteristic pattern of staining for measles virus was observed in the tissues of some affected children at a significantly higher rate than developmentally normal pediatric controls. The staining pattern was consistent with the follicular dendritic cell (FDC) matrix, as seen in HIV infection. Similar staining for other viruses was not seen. Measles virus Fusion (F) gene genomic RNA was identified by TaqMan RT-PCR in 75 (82%) of 91 children with ASD and 5 (7%) of 70 developmentally normal controls, confirming an association between the presence of measles virus and gut pathology in children with developmental disorder (113). In seeking to determine strain specificity, O’Leary and colleagues developed an allelic discrimination (AD) assay, based upon the data of Parks et al. (114), that exploits an A to C base-change from Edmonston wild-type to Edmonston-derived strains at position 7901 in the HA-gene resulting in a predicted serine to glycine
substitution at amino acid position 211 of the measles virus. In this way, all 50 HA-gene amplicons obtained from affected children were shown to be consistent with the vaccine strain (115).

Several of the authors (SW & AK) have sought to replicate these findings in an independent population of children with a similar constellation of GI and developmental symptoms (116). All children had received MMR vaccine as their only documented exposure to measles virus. Ileal biopsy tissue was assayed by nested RT-PCR for the presence of measles virus RNA and PCR-positive samples were sequenced. Analysis of initial 82 patients showed that 70 (85%) were positive for the F-gene amplicon. Fourteen had been verified by DNA sequencing which was pending for the remaining amplicons at the time of publication. Preliminary results from this large cohort of pediatric autistic patients with chronic GI symptoms confirm earlier findings of measles virus RNA in the terminal ileum and support an association between measles virus and autistic enterocolitis.

While presence of viral RNAs in diseased tissue is not proof of causation, its absence is not proof of lack of causation. Samples are taken, often many years after MMR exposure and autistic regression has occurred; neurologic injury may be effected within a critical window of viral presence. In support of this, a recent report has shown a statistically significant association between recovery of cognitive skills and absence of measles virus RNA in ileal lymphoid biopsy and therefore, possible viral clearance (117). Ref needs to go in

**Viral serology** In a series of studies of similarly affected children from the US, Singh et al. have identified quantitative and qualitative differences in the IgG
antibody response to measles virus (70,118,119) compared with developmentally normal populations. Anti-measles virus IgG antibody levels are significantly higher in the blood of affected children compared with developmentally normal children of the same age, and sibling controls. This was not the case for IgG antibodies against rubella virus and mumps virus. In addition, immunoblotting studies identified a specific IgG antibody response in 80 per cent of affected children to a 74kD protein antigen from the measles virus HA-protein derived from the MMR vaccine that was not detected in any controls.

In children examined in a UK pediatric clinic, serum IgG immunoreactivity for measles virus was significantly elevated in autistic children referred with GI symptoms, compared with children of a similar age; mumps, rubella and cytomegalovirus IgG antibody titres were not similarly elevated (120).

The data confirm an association between measles virus and GI pathology in some children with developmental disorder, particularly regressive autism. The presence of the virus may reflect a bystander effect due to sequestration of measles virus in foci of activated lymphoid tissue, although this is unlikely, due to its absence from inflamed pediatric control tissues. In view of the presence of both measles virus antigen and genomic RNA in reactive lymphoid tissues, it is also unlikely that the observations indicate long term trapping of viral antigen by FDC, as part of a normal immunological process. The interpretation of the findings in mucosal biopsies is not mitigated by failure to identify measles virus in peripheral blood mononuclear cells (121). Needs to go in.
The data indicate that the intestinal mucosa may be a source of persistent infection and hence possible shedding of measles virus. Is there any evidence for the latter occurring in the context of autistic enterocolitis?

**Horizontal transmission: further evidence from autistic enterocolitis**

Further evidence of horizontal transmission of measles vaccine virus has come from several sources. We are aware of an increasing number of siblings of children affected by autistic enterocolitis, onset of which followed MMR vaccine exposure. For reasons of parental concern, these siblings did not receive MMR or any other measles-containing vaccine; nor did the sibling have any documented exposure to natural measles. These siblings are, however, seropositive for measles, often at high titer and on repeated measurement. Some suffer GI and/or behavioral symptoms while others are asymptomatic. Given the wide geographic distribution of these cases and lack of any other mode of exposure, it is likely that these children were infected horizontally from their vaccinated autistic sibling.

Further evidence in support of this observation has come from a large preliminary study by one of the authors [PA] who has conducted a large serological analysis of IgG titers to vaccine exposures (measles, mumps, rubella, diphtheria, tetanus, and pertussis) and natural viral exposures (cytomegalovirus, and influenza A and B) (122). Importantly, study populations were segregated into: children with an autistic spectrum disorder, their siblings, unrelated general population controls, and developmentally normal children with atopic disease. Consistent with the observations elsewhere of immunodeficiency in the autistic population, total IgG, IgA, and IgM titers were significantly decreased in ASD children compared with the other groups. In the study as
presented (following correction of the data presented initially in the abstract).

Antibody titers to all antigens except measles and rubella were significantly lower in the ASD children compared with other groups, a finding that may reflect the low total serum IgG in these children. Paradoxically, measles and rubella IgG titers were significantly greater in the ASD children, despite low total IgG, compared with the general population and atopic disease control groups. The data provide independent support for the observations of Singh and colleagues. Crucially, and in contrast with the general population pediatric controls, measles virus IgG titers in unaffected siblings were very similar to the ASD population.

There are several explanations for these findings, including a similar genetically-determined antibody response to the vaccine between affected children and their siblings. Alternatively, the data are consistent with antibody boosting following re-exposure of the siblings through episodic horizontal transmission from affected siblings. The findings are consistent with the phenomenon of antibody boosting following subclinical exposure, based upon similar observations of Pederson et al in Greenland natives (38).

**Molecular evidence of horizontal transmission in autistic enterocolitis**

As part of a viral replication study of autistic enterocolitis, performed by two of the authors (AK and SW) measles virus genomic RNA was identified in the ileal lymphoid tissue of an MMR-vaccinated child with onset of autistic regression following vaccination. This child was found to have mucosal pathology consistent with autistic enterocolitis. Their younger sibling was unvaccinated, had no documented exposure to natural measles, and yet suffered from an ASD and GI symptoms. RT-PCR analysis of this child's ileal
lymphoid tissue similarly revealed the presence of measles virus RNA. This sentinel case provides clear evidence, not only of horizontal transmission of the vaccine virus, but also indicates the possibility of the emergence of a gut-adapted pathogenic variant.

**Implications for neo-pathogenesis, epidemiologic predictions and disease phenotype**

Compared with the typical pattern of natural exposure, infants are now exposed to measles virus by a different route, using a different strain, and at a different mean age and intensity compared with their ancestors. The additional implications of viral interference for increasing risk of persistent infection and delayed disease in combination vaccines, is not known. Concern is raised at the possibility that neopathogenesis – persistence of the virus in intestinal tissues associated with an emergent chronic immunopathology – may be one result. Once horizontal transmission has started there is no model – since there are no data- that enables prediction of the impact upon measles infection or associated rates of conditions such as autistic enterocolitis. The potential for shedding and horizontal transmission of a gut-adapted pathogenic clade A measles virus would make redundant, published epidemiologic efforts to examine risk and associations based upon records of vaccine exposure (79,123) or temporal trend analyses comparing autism rates with MMR uptake at the population level (124-126). At the very least, serologic analysis of unvaccinated populations would be necessary in an effort to assess exposure status. This, too, may be imperfect if horizontal transmission occurs in infants protected by maternal immunity in whom there is consequent failure of seroconversion.
Caution would also be necessary in phenotyping of, for example, subpopulations of autistic individuals. The recognition of developmental traits such as ‘early-onset’ and ‘regressive autism’, is starting to influence perception of how investigation of distinct autism subsets, with presumed differences in etiology, might advance research into understanding cause. Such a perception will be of limited merit if transmission from an affected child who regressed after MMR vaccination, is subsequently able to shed pathogenic measles virus to a younger close contact who then acquires the disease at an age that classifies him as ‘early onset autism’.

**Siblings are not controls**

Given the potential for transmission to close personal contacts, siblings - whether healthy or symptomatic - cannot be considered controls in studies that examine aspects of disease pathogenesis and etiology that may be related to, for example, measles virus exposure and its potential immunologic and other consequences. Interpretation of hereditability studies will need to be modified, taking into account the potential for transmission of a possible causative agent from older siblings in particular, combined with the lower chance of disease expression in female pairs of mixed-sex twin pairs. The latter issue would be relevant to the interpretation of disease concordance in monozygotic versus dizygotic twins.

**Implications for surveillance, control, and eradication of measles virus**

Measles control strategies are based upon the assumption that measles virus transmission occurs in chains of transmission of clinically recognizable measles cases (127). As such, surveillance is limited to the identification of persons meeting the case definition of measles, that is, generalized maculopapular rash
lasting for 3 or more days, a fever of 38.3°C or higher, and cough, coryza or conjunctivitis (128). However, the occurrence of measles virus infections in persons without classical measles (including, therefore, the majority of vaccinees) may play an important role in the transmission if measles. Serologic evidence of acute measles has been documented among people who are exposed to measles virus but do not develop classical symptoms (128-136). This phenomenon has been observed most frequently in highly vaccinated populations with rates of infection of 4%-42%.

Liveano et al referred to these cases as ‘inapparent’ measles infections, a nomenclature that is adopted here, and raised the issue that such infections could be epidemiologically important if infected persons are capable of transmitting measles virus (127). However, they failed to recognize that inapparent measles infection may include not only asymptomatic and minimally symptomatic disease, but also neo-pathogenetic disease symptoms that fall outside the case definition, such as the diarrhea associated with autistic enterocolitis. The authors consider that respiratory contagion is a “presumed requisite for transmitting the virus”. This makes little sense for vaccine virus transmission, since subcutaneous injection bypasses the initial phase of viral replication and shedding in the respiratory tract. Some of the authors have documented urinary shedding of both wild-type and vaccine virus, and fecal shedding does not appear to have been examined.

Liveano et al sought to establish whether persons with inapparent measles – based upon serum IgM response on days 12-16 following known exposure to a measles case – were capable of subsequent shedding of virus in urine and nasopgarangeal swabs (127). Eight percent of 133 exposures with inapparent
measles exhibited a diagnostic IgM response. Duration of exposure of 3 hours or more was the only significant risk factor for developing a positive serologic response, where the positive rate rose to 24%. Virus was not recovered by culture or RT-PCR in any of those with inapparent infection.

While these findings provide some reassurance that some persons with inapparent infection do not subsequently shed virus during the limited observation period, it is apparent that the great majority, if not all, of the contacts were already immune to measles. As such, their secondary immune response would have been a major impediment to viral replication and shedding. The findings, therefore, bear little relevance to the potential for virus shedding in non-immune contacts, such as unvaccinated infants, who develop inapparent measles, whether asymptomatic or neo-pathogenic. In the case of the latter, the data indicate that children with autistic enterocolitis are capable of shedding measles vaccine virus. Those exposed, such as siblings, are inevitably in contact for well in excess of the 3 hour ‘intensive exposure’ window reported by Liveano et al, and therefore at considerable risk of infection.

**Persistent infection and waning immunity**

The possibility that measles outbreaks may occur from a point source such as persistently infected individual in whom immunologic surveillance has failed, either due to waning of vaccine-induced immunity over time, or intercurrent immunodeficiency, for whatever reason, is a concern shared by Pütz et al (14). This may become increasingly important in acquired immunodeficiency states such as HIV, and the setting of organ, bone marrow, and stem cell transplantation. The associated immunodeficiency in children with autism and autistic enterocolitis, in particular, with immunoglobulin deficiency,
lymphopenia, impaired NK cell cytotoxicity (137 & Vojdani A et al; unpublished data), and possible cytotoxic T-cell exhaustion, may provide a reservoir of individuals capable of initiating such outbreaks.

Horizontal transmission of measles vaccine virus is a serious threat to efforts at global measles eradication. Mathematical modeling has suggested that eliminating measles would be impossible if measles virus can be transmitted in the absence of classical measles disease (138). This was considered to be the case even though the model of Mossong et al did not take account of a neo-pathogenetic source of transmissible virus. Pütz et al observe that, 'in the final stages of an eventual measles elimination program, the reintroduction of a circulating vaccine strain which has (partially) lost attenuation could be a serious threat' (14). While the meaning of 'an eventual measles eradication program' is somewhat obscure, it is clear that such an intention would be thwarted by the emergence of horizontally transmitted vaccine virus. Why this concern should be confined to the eventual stages of such a program is not clear.

Conclusion
This review has taken the position that: outbreaks of likely vaccine-associated measles virus occur; measles-containing vaccine exposure is associated, in some children, with neo-pathogenesis – particularly enterocolitis that may be associated with an autistic encephalopathy; and that horizontal transmission of measles vaccine virus may operate in both the affector and effector paths of this neo-pathogenetic process. Evidence for these processes is emerging in both human and non-human primate settings. Confirmation of such horizontal transmission and neo-pathogenesis would send epidemiologists back to the drawing board. The implications of horizontal transmission and
neopathogenesis for measles surveillance, control, and eradication are far-reaching.

This above perception will be considered to be controversial. However, the data indicate that reliance can no longer be placed on the position taken obversely, by Katz and colleagues in their dismissal of indications of horizontal transmission in early clinical trials. In the inevitable schism of bias there is a lesson to be learned: in the crucial issue of vaccine safety, particularly as more and more vaccines are queued-up for licensing and inclusion in mandatory vaccine programs, responsibility for evaluation, interpretation and both short and long term monitoring of vaccine safety issues should fall wholly under the jurisdiction of an independent agency. This agency should be completely devolved in terms of accountability, resourcing, and oversight, from those agencies and interests responsible for soliciting, funding, endorsing, and profiting from, vaccines. The new agency should permit no conflict of interest internally. Only in this way will the concerns of the consumer and the long term interests of public health start to be best-served.

**Key words:** autism, autistic enterocolitis, fecal transmission.

**Acknowledgements:** This work was funded by the Johnson Family Foundation and The Ted Lindsay Foundation.

**Disclosures:** AJW, AK and PA have acted as paid experts in MMR-related litigation. AW in a named inventor of two viral diagnostic patents.
References


21. Riddell MA, Rota JS, Rota PA. **Review of the temporal and geographical** distribution of measles virus genotypes in the pre-vaccine and post-vaccine **eras.** Virology Journal. 2005, **2:**87-92


23. Rota PA, Bellini WJ. **Update on the global distribution of genotypes of wild type measles virus.** J. Infect. Dis. 2003, **187:**S270-S276.

24. Chen P, Miller GF, Powell DA. **Colitis is a female tamarin (Saguinus mystax).** Contemporary Topics: American Association of Laboratory Animal Scientists. 2000, **39:**47-49.


27. Lednicky JA, J. Dubach TP, Meehan MJ, Kinsel M, Bochetta LL, Hungerford NA, Sarich KE, Witecki MD, Pedrak CB, Houde CM. Genetically distant American Canine distemper virus lineages have recently caused epizootics with somewhat different characteristics in raccoons living around a large suburban zoo in the USA. Virol. J. 2004, 1, 2 (volume 1, article 2).


32. Steinworth-Goetz I, Amild U. Life and belief of the forest Waïka in the Upper Orinoco. Translated by Furst P. Caracas: Asociació́n Cultural Humboldt, 1969: p.56

34. “It is very difficult for me to give you a reasonable comparative clinical impression of the young Brazilian I saw at Ocamo. There is no question that he was very sick; he kept a temperature in the vicinity of 40°C for more than a week, he obviously had bronchopneumonia and he was prostrated. He was approximately 14 years old.” Marcel Roche, letter to James Neel, April, 1968.


38. “As a representative of the community I want to give my word so that you know what has happened with the anthropologists---that is, the real truth. ....Our people did not know how to speak well and did not understand anything that was happening and what they were doing with the people. They believed they were doing good to the people, but, on the contrary, their actions were evil. And as they explained that the vaccine was not to become ill, they believed it. Afterwards, they started to get sick. First, one became ill and soon
all the others were infected. The people fled from Chagnon who brought the
disease. And the nurse who was supposed to stay in the community came and
went, but did not stay put. That's how it started. Others became lost in the
mountains and nobody in their family knew about it until they were found
dead.” Alfredo Aherowe, Yanomami, elected representative of the United
Shabonos of the Upper Orinoco, testimony to the Comision Indigena del

geography of a major human viral disease from global expansion to local

40. Pedersen IR, Mordhorst CH, Evald T, von Magnus H. Long-term
antibody response after measles vaccination in an isolated Arctic society

41. Pedersen IR, Mordhorst CH, Glikman G, von Magnus H, Subclinical
measles infection in vaccinated seropositive individuals in Arctic

42. Wakefield AJ, Pittilo RM, Sim R, Cosby SL, Stephenson JR, Dhillon AP,
Pounder RE. Evidence of persistent measles virus infection in Crohn's

43. Miyamoto H, Tanaka T, Kitamoto N, Fukada Y, Shimoyama T. Detection
of immunoreactive antigen with a monoclonal antibody to measles virus


49. Pardi DS, Tremaine WJ, Sandborn WJ, Loftus EV, Poland GA, Harmsen WS, Zinsmeister AR, Melton LJ. Early measles virus infection is associated
with an increased risk of inflammatory bowel disease. Am J Gastroenterol. 2000, 95:1389-1392


95. Molloy CA, Morrow AL, Meinzen-Derr J, Schleifer K, Dienger K, Manning-Courtney P, Altaye M, Wills-Karp M. Elevated cytokine levels in


108. Ke ZJ, Bowen WM, Gibson GE. **Peripheral inflammatory mechanisms modulate microglial activation in response to mild impairment of oxidative metabolism.** Neurochem Int. 2006; 49:548-56


115. Sheils O, Smyth P, Martin C, O’Leary JJ. **Development of an allelic discrimination type assay to differentiate between the strain origins of measles virus detected in intestinal tissue of children with ileocolonic**


