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Measles Vaccines
A Review of Adverse Events

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Contents

Abstract

A great deal of controversy has recently been generated over the publication of several articles implicating measles vaccine in the induction of Crohn's disease and autism. The publication of this work has already had a negative impact on measles vaccine acceptance in the UK. These allegations are particularly troubling because they arise in the context of increased use of measles vaccine as global control of measles nears and the international community considers strategies for a drive towards eradication.

In 1994, the US Institute of Medicine reviewed the world literature and published a comprehensive review of adverse events associated with measles-containing vaccines. Reviewing the literature published between 1994 and the

present day, reveals that there is considerable new data suggesting that modified gelatin rather than egg proteins is responsible for most episodes of anaphylaxis following measles vaccination. New work weakens the possible links between measles vaccine and subacute sclerosing panencephalitis and Guillain-Barré syndrome, but strengthens the rare association of measles-containing vaccines with post infectious encephalomyelitis. The alleged associations between measles vaccination and Crohn's disease and autism are based upon weak science and have largely been refuted by a large volume of stronger work.

A review of the data generated in the last 4 years amply demonstrates the continued efforts of the scientific community to monitor and understand true measles vaccine-associated adverse events. The rapidity and clarity of this same community's debunking of the spurious associations with Crohn's disease and autism suggests that those charged with vaccination programmes have learned from past mistakes.

During 30 years of worldwide use, measles vaccination has proven to be one of the safest and most successful health interventions in the history of mankind. It is not a 'perfect' vaccine, but the benefits of measles vaccination far outweigh the risks even in countries with low incidence of measles and high rates of measles vaccine coverage.

1. Background

The recent years have witnessed important changes in measles control. Although measles still claims the lives of nearly 1 million children (primarily in Africa and Asia) and infects more than 40 million children each year, much progress has been made. Measles immunisation is estimated to save 2 million lives each year. In 1990, the World Summit for Children announced a goal of reducing measles cases by 90% and measles deaths by 95%, compared with pre-immunisation levels, by the year 2000.[1] Although not without difficulties, this goal now appears achievable.

In 1994, the Ministers of Health of the American Region established the goal of eliminating measles virus from the Western Hemisphere by the year 2000.[2] Strategies recommended by the Pan American Health Organization to achieve this goal included short term national immunisation campaigns aimed at immunising all children between 1 and 15 years old regardless of previous measles vaccination status, and the maintenance of high immunisation coverage through routine immunisation. Member countries have made significant progress toward measles elimination through a strategy combining periodic mass vaccination campaigns as complements to routine vaccination services (adopted by most countries) or the implementation of 2-dose measles immunisation schedules with (Canada) or without (USA) a 1-time catch-up campaign.

Several countries outside the Americas have also implemented mass catch-up campaigns in recent years (in the context of which many children receive a second dose of vaccine) or implemented routine 2-dose immunisation schedules to overcome primary vaccination failures. These intensified efforts at measles control have resulted in a large increase of measles vaccine utilisation worldwide. At an international meeting in Atlanta in 1996, participants agreed that measles eradication was technically feasible within the next 15 years.[3]

In this context of a drive towards measles elimination and increased vaccine use, much controversy has recently been caused by suggestions that measles vaccine can cause Crohn's disease[4] and more recently autism.[5] On the one hand, these allegations generated concerns in all sectors about measles vaccine safety (if true). On the other hand, those charged with vaccination programmes immediately recognised that, even if false, these allegations had the potential to decrease vaccine acceptance. Indeed, in the UK, where the researchers live and where the research findings concerning

Crohn's disease and autism where first published, measles, mumps and rubella (MMR) vaccine coverage was documented to fall.[6] Fears were raised that history would repeat itself in the UK where unfounded concerns about the pertussis vaccine in the 1970s led to a decreased vaccine coverage resulting in thousands of pertussis cases and hundreds of unnecessary deaths.

This paper presents a comprehensive review of new information pertaining to adverse events associated with measles-containing vaccines and discusses the risks and benefits of measles vaccination. The review does not discuss adverse events related to the killed measles vaccine since these have been well described[7] and it has been nearly 30 years since the use of this vaccine was stopped.

The review also excludes adverse events associated with the use of experimental vaccines (i.e. intranasal) or high titre vaccines. Use of the latter vaccines was stopped in 1993 after reduced survival benefits for girls were reported in some countries.[8-13] Interested readers are referred to the cited work regarding high titre vaccines as well as recent efforts at understanding the pathogenesis of measles and measles vaccines in general.[14-18]

Our review also does not cover adverse events associated with MMR vaccination that are known to be related to either the mumps, e.g. aseptic meningitis with the Urabe strain,[19] or the rubella components, e.g. arthropathy in nonimmune women ≥20-years-old, of the trivalent vaccine.[20-23] Finally, the review does not deal with the potential adverse events associated with measles vaccine which could be caused by inappropriate handling including reconstitution with the wrong diluent, contamination,[24] or errors in production.

2. Methods, Sources of Information and Changes in Situation

In response to concerns about vaccine safety, the US Congress passed the National Childhood Vaccine Injury Act in 1986 and the Vaccine Compensation Amendments in 1987. These laws created a federal, no-fault compensation programme and requested a comprehensive scientific review of the possible adverse events associated with common childhood vaccines. The Institute of Medicine of the National Academy of Sciences, an independent scientific organisation, was mandated under the Act to conduct this review. The results were published in 2 volumes covering pertussis and rubella vaccines in 1991[25] and the remaining childhood vaccines including measles in 1994.[19]

In developing its reports, the Institute of Medicine reviewed the world medical literature, obtained information from medical experts and conducted public meetings to gather information. Persons alleging vaccine-related injuries were allowed to participate in the public meetings. Since the Institute of Medicine report was published in 1994,[19] our literature search was limited to articles published after 1994. Relevant information from other sources such as discussion groups and advisory committees documents were also scrutinised.

In addition, the database of the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring, Uppsala, Sweden was searched for adverse events reported following the use of a measles-containing vaccine. Around 40 countries participate in this passive reporting programme in which adverse events temporally associated to vaccines are forwarded to the WHO database without any consideration of causality.

Although the reporting of vaccine-associated adverse events has historically been limited to passive surveillance, many countries have recently committed new resources to strengthening both active and passive monitoring. This has been particularly true in the context of mass measles vaccine campaigns and the initiation of programmes to deliver a second dose of measles vaccine to large numbers of children and adolescents. In addition, viral sequencing has proved to be a very powerful tool for distinguishing between wild-type and vaccine-strain virus in the rare circumstances in which measles virus has been isolated or measles genetic information has been recovered associated with a purported adverse event.

Before discussing individual measles vaccine–associated adverse events we believe that it is important to describe the components of measles vac-

cine since several of the nonviral components may plausibly contribute to the risk of adverse reactions.

3. Measles Vaccines and Their Content

3.1 Intentional Content

Most measles vaccines in current use (Moraten [Enders-Edmonston] and Schwartz vaccines) are attenuated and are produced in chick embryo fibroblasts, although some are attenuated and grown in human diploid cells (as in the case of the Edmonston-Zagreb vaccine). Minor differences exist among manufacturers of vaccines as regards dose [1000 to 20 000 Cell Culture Infectious Doses 50 ($CCID_{50}$) for regular titre vaccines[26]], antibiotic content, and minor components. Although significant differences in adverse events or vaccine efficacy have not been reported, it is not impossible that such differences exist.

Production of vaccine-strain virus typically begins with inoculation of a susceptible cell culture in a growth media containing fetal bovine serum and antibiotics. After incubation for several days, the cells are washed to remove fetal bovine serum, and the media is replaced with one containing neomycin 50 mg/L, sucrose, buffered salts, amino acids and human albumin. Culture supernatants containing the virus are removed periodically over 24 to 36 hours of peak production and frozen. Supernatants that have sufficient potency are thawed, pooled, sampled for safety testing, clarified, dispensed and refrozen. When bulk vaccine has passed all quality control tests, portions of the vaccine are thawed, dispensed into vials and lyophilised. At the time of use, the vaccine is reconstituted with sterile distilled water (the vaccine should only be reconstituted with the diluent supplied by the manufacturer).[24] Each dose contains approximately 25μg of neomycin and small amounts of sorbitol and hydrolysed gelatin which are added as stabilisers.[7]

3.2 Unintentional Content

In 1996, using a test 1-million times more sensitive than previous tests, scientists in Switzerland reported finding very small quantities of reverse transcriptase activity in several live viral vaccines produced in chick embryo fibroblasts (yellow fever, measles and mumps vaccines).[27] Although reverse transcriptase itself poses no known risk to humans, there was some concern that the presence of the enzyme might indicate the presence of 1 or more retroviruses which could possibly infect and cause illness in humans.

The source of this particle-related enzyme activity has subsequently been shown to be endogenous avian retroviruses which are carried as 'normal' chicken genes, and are believed to have existed in this form for millions of years. Molecular characterisation of viral genetic material in the vaccine harvest from chick embryo fibroblasts identified the presence of both endogenous avian virus and to a lesser extent endogenous avian leucosis/sarcoma virus–related sequences associated with the particles.[28,29] Preliminary sequence studies indicate that the particles are defective, e.g. incomplete genome.[28]

There is no evidence that the presence of these viral gene segments has any health significance. Extensive studies in several laboratories have investigated the infectivity of the particles. This has included extensive passaging and co-cultivation with more than 14 different cell types including human peripheral blood mononuclear cells. In no case could productive infection be demonstrated.[28,30-32] Limited studies of the sera of vaccinees did not reveal immunological response to avian retroviral antigens and no retroviral sequences were found in peripheral blood mononuclear cells of vaccinees.[28]

Finally, tens of thousands of persons who received yellow fever vaccines known to contain avian retroviruses during World War II do not appear to be at increased risk for leukaemia, lymphoma or other cancer.[33] Other current epidemiological studies reveal no association between the use of chick embryo fibroblast–derived vaccines and an increased incidence of cancer.[28] Following a recent extensive consultation which took place in April 1998, the WHO recommended continuation of chick embryo fibroblast–derived vaccine use and will be monitoring new developments.[29]

3.3 Vaccination Programmes

Measles vaccine is commonly administered either as monovalent measles or combined triple MMR vaccines. Most of the developing world and economically disadvantaged countries use only monovalent measles vaccines whereas most of the countries with more ample resources use MMR vaccines. Limited quantities of measles-rubella vaccine have also been used in recent years, particularly in the context of combined catch-up campaigns for measles and rubella immunisation.

In developing countries where measles remains endemic, measles vaccine is generally administered at 9 months of age. In other countries, where measles incidence and the risk of measles complications are lower, vaccine is generally administered after 12 months of age or even later (15 or 18 months) in order to maximise vaccine effectiveness. The age at which a routine second dose (if part of the regular schedule) is administered varies, e.g. 18 months, preschool, beginning of secondary school, depending on the strategy adopted. Mass catch-up campaigns have generally targeted preschool children although many programmes have covered school-age children as well.

The dramatic increase in measles vaccine usage in the last few years associated with mass campaigns, catch-up campaigns[1] and the implementation of 2-dose schedules has focused a great deal of attention on the known and potential adverse events associated with this vaccine. Several countries and jurisdictions have taken advantage of this increase in vaccine usage to actively monitor adverse events associated with measles-containing vaccines in a more intense fashion. Overall, the data accruing from this enhanced surveillance is reassuring.[34,35]

4. Expected Adverse Reactions

Measles vaccine contains 1000 to 20 000 $CCID_{50}$ of an attenuated virus which can and does infect a wide range of human tissues. Therefore, it is not surprising that up to 5% of nonimmune vaccinees develop moderate to high fever ≥38.6°C within 7 to 12 days of immunisation. This vaccine-induced fever typically lasts 1 to 2 days and causes little disability. Generalised, transient rashes and conjunctivitis due to vaccination have also been reported; these adverse events occurred in approximately 1.6 and 2.1% of vaccinees, respectively, in a double-blind, placebo-controlled, crossover study.[36] Simple febrile seizures occur infrequently after measles or MMR vaccination and generally have no sequelae. An increased risk of febrile seizures may occur in children with a personal history or first-degree family history of seizures.[37]

By linking vaccination records with computerised hospital admission records in 5 districts in the UK, Farrington et al.[38] suggested that 67% of admissions for a febrile convulsion 6 to 11 days after MMR vaccination were attributable to the measles component of the vaccine (risk 1 in 3000 doses). Because the period of greatest risk for measles vaccine–induced fever is delayed after vaccination, prevention of vaccine-associated febrile seizures is difficult. Prophylaxis with antipyretics has been suggested, but treatment would have to be initiated before the expected onset of fever and continued for up to 5 to 7 days.

Nonetheless, parents should be alert to the occurrence of fever after vaccination and treat their children appropriately. Children with seizure disorders treated with anticonvulsants should certainly continue taking these medications after measles vaccination. Parents of children with either a personal or family history of seizures should be advised of the small increased risk and be given explicit instructions for treatment should a seizure occur.[39]

5. Unexpected Adverse Reactions

5.1 Anaphylaxis

Evidence included in the Institute of Medicine review establishes a causal relationship between MMR vaccination and anaphylaxis and favours acceptance of a causal relationship between measles vaccine and anaphylaxis. Although no reliable estimates of the incidence or relative risk (RR) of anaphylaxis were available, estimates from case reports, case series and noncomparative observational studies ranged from 1 per 20 000 to 1 per

million doses distributed.[19] Although it has long been believed that anaphylaxis following measles-containing vaccines is due to egg allergies, recent work demonstrates the relative safety of MMR vaccination in children with egg allergies and questions the value of the skin testing with MMR vaccine. We now have a better understanding of the component of measles-containing vaccines most likely to be responsible for anaphylactic reactions.

5.5.1 Egg Allergy

The literature contains reports for more than 1200 individuals with egg allergies who have been assessed for measles immunisation. Routine immunisation was tolerated in all of the 1209 (100%) children with positive skin tests for egg allergies [95% confidence interval (CI) 99.75 to 100] and in 1225 out of 1227 (99.8%) children with histories of egg allergy (95% CI 99.41 to 99.98).[40]

In a study of 500 children with egg allergy, Freigang et al.[41] reported that even those children with a documented history of anaphylaxis to eggs (n = 33) could be safely vaccinated with MMR. It has been repeatedly demonstrated that the results of prick and intradermal testing with MMR have little bearing on the final reaction to MMR.[39,40,42]

Although some investigators still recommend skin testing for MMR in children with egg allergy,[43] in our view they typically do so on the basis of limited or no information regarding which component of the vaccine actually causes the reaction.

Finally, a total of 38 anaphylactic reactions after measles immunisation have been reported in the literature in individuals without a history of egg allergy. In view of these data, the Canadian National Advisory Committee on Immunisation has recently recommended that egg allergy should no longer be a contraindication to immunisation with MMR. However, a previous anaphylactic reaction to a measles-containing vaccine remains a contraindication.[44]

5.1.2 Allergy to Other Components

Although neomycin and the measles proteins themselves are possible allergens, the lack of prior exposure at the time of routine vaccination and the tiny quantities of these proteins in measles-containing vaccines make them unlikely candidates to trigger an anaphylactic reaction.[40] The carbohydrate sorbitol is not known to elicit any immune reaction. The most likely culprit is, in fact, hydrolysed gelatin. In a case-control study of 26 children with systemic immediate-type reactions, including anaphylactic shock, to measles (n = 24), mumps (n = 1) or rubella (n = 1) vaccines and an equal number of control individuals, Sakagushi et al.[45] were able to show a strong relationship between immediate-type, systemic allergic reactions and the presence of gelatin-specific immunoglobulin (Ig) E. Measles vaccines from a wide variety of manufacturers typically contain 1.5 to 10mg of bovine or porcine gelatin or polygeline (a polymer of bovine gelatin) per dose.

5.2 Encephalopathy/Encephalitis and Residual Seizure Disorders

Natural measles virus infection causes post-infectious encephalomyelitis in approximately 1 per 1000 infected persons. At least 50% of those affected are left with permanent central nervous system impairment. This syndrome is considered to be immunologically mediated because of the perivenular demyelinating lesions. Genetic susceptibility to post-infectious encephalomyelitis has been postulated but not proven.[46]

Whether or not the strain of virus in the measles vaccine could also produce such a syndrome has been a concern since the introduction of measles vaccines. In 1994, the Institute of Medicine noted that most data were from case reports, case series, or noncomparative observational studies and concluded that the evidence was inadequate to accept or reject a causal relationship between measles vaccination and post-infectious encephalomyelitis.[19] The incidence of encephalitis after measles vaccination of healthy children tends to be lower than the observed incidence of unknown aetiology.[36] The Institute of Medicine committee came to the same conclusion with respect to the possible association between measles vaccination and residual seizure disorders.[19]

Two large studies published since 1994 have supported the Institute of Medicine's conclusions.

Based on the British Childhood Encephalopathy Study, Miller et al.[47] conducted a case-control study of the relationship between administration of a measles-containing vaccine and the onset of acute encephalopathy in previously healthy participants (those with febrile convulsions were excluded). They found no increased risk for either encephalopathy [RR = 1.22 (95% CI: 0.43 to 3.47)] or neurological sequelae [RR = 0.84 (95% CI 0.2 to 3.49)] after measles vaccination. The validity of the study was debated but was satisfactorily defended by the authors.[48,49]

Through the Vaccine Safety Datalink project which collects computerised vaccination and medical outcome data from 4 large Health Maintenance Organisations, Black et al.[50] conducted a retrospective case-control study to assess the risk of hospitalisation for aseptic meningitis within 30 days of receiving MMR. No such risk was identified for the 300 000 doses of MMR administered during the study period. Although this study was not intended to evaluate the risk of encephalopathy after vaccination, not a single case of encephalopathy or encephalitis occurred within 30 days of receiving the MMR vaccine.

In contrast, a third group has recently reported a positive association between measles vaccine and encephalopathy. Weibel et al.[51] reviewed claims submitted to the US National Vaccine Injury Compensation Program. They identified 48 children who developed encephalopathy with no determined cause within 15 days of receiving the first dose of measles-containing vaccine between 1970 and 1993. The onset of symptoms occurred with a statistically significant nonrandom distribution in 17 children on days 8 and 9. The authors concluded that, since there was an equal likelihood of patients being compensated by the programme if the encephalitis occurred at any time within 15 days, their findings suggested a causal relationship between measles vaccine and encephalopathy. Although bias cannot be totally ruled out in this study (i.e. passive reporting system), the compensation programme is well known and generous, suggesting that most of the serious cases of encephalopathy experienced during this period would have been reported.

In Canada, only 1 out of 7 children who were reported to have developed acute encephalitis after the administration of a measles-containing vaccine between 1991 and 1996, and for whom causality was not rejected by the Canadian Advisory Committee on Causality Assessment,[52] experienced the long term sequelae of a mild seizure disorder (P. Duclos, unpublished observations). It must, however, be noted that this child had bilateral hippocampal signal abnormalities and that a younger sibling with the same central nervous system abnormality also had seizures. Because Canada has an active surveillance system in all paediatric hospitals which looks specifically for encephalopathy and encephalitis occurring within 30 days of immunisation,[53] it is unlikely that a significant number of severe cases would be missed.

5.3 Sensorineural Deafness

In 1994, the Institute of Medicine concluded that the evidence was inadequate to accept or reject a causal relationship between measles vaccine and sensorineural deafness.[19] Recently, Jayarajan and Sedler[54] have added another case report to the limited literature. In their discussion, the authors support their contention of a biologically plausible link by quoting a chapter in a textbook[55] in which it was stated that 5 to 10% of sensorineural hearing loss in children is attributed to natural measles. The author of this chapter, however, provides no references to support this statement.

5.4 Optic Neuritis

The biological plausibility of a causal relationship between optic neuritis and measles vaccine is based on the observation that natural measles virus can induce a demyelinating disorder, i.e. postinfectious encephalomyelitis. In 1994, the Institute of Medicine concluded that evidence was inadequate to accept or reject a causal relationship between measles vaccine and optic neuritis.[19] The number of reported cases was too small and the data contained within these reports were too limited to prove a positive association.

Since the Institute of Medicine report, only 2 cases of optic neuritis have been reported and in

these children the optic neuritis occurred 18 and 21 days following administration of measles-rubella vaccine.[56] Both of these cases occurred in the midst of the mass immunisation campaign in the UK in which over 6 million doses of measles-rubella vaccine were administered making temporal and purely fortuitous associations likely.

5.5 Subacute Sclerosing Panencephalitis

Subacute sclerosing panencephalitis is a rare and progressive encephalitis which is inevitably fatal. There is no question that the wild-type measles virus causes subacute sclerosing panencephalitis since a heavily mutated virus can be 'rescued' from patients with subacute sclerosing panencephalitis. As a result, it is biologically plausible that there might be a link between vaccine strain virus and subacute sclerosing panencephalitis or a subacute sclerosing panencephalitis–like condition. Since the incidence of subacute sclerosing panencephalitis has decreased dramatically in parallel with widespread measles immunisation, any such risk would have to be very small compared to the association with natural disease. In 1994, the Institute of Medicine committee concluded that the evidence was inadequate to accept or reject a causal relationship between measles vaccine and subacute sclerosing panencephalitis.[19]

Despite the compelling inverse relationship between vaccine usage and subacute sclerosing panencephalitis incidence, at the first International Public Conference on Vaccination in 1997, put together by the National Vaccine Information Center, concerns were raised that measles vaccination may exacerbate existing subacute sclerosing panencephalitis and that a second dose of vaccine may be more likely to initiate subacute sclerosing panencephalitis than the first.

According to the transcript of a speech given at this conference, in our view many unsubstantiated allegations were made. These allegations included an affirmation that measles vaccine can cause subacute sclerosing panencephalitis and the statement that vaccine-induced subacute sclerosing panencephalitis occurs with a shorter pre-patent period (3 months versus 6 years for natural disease). Although these allegations are not new and were abundantly discussed and rejected in the 1994 Institute of Medicine report,[19] we will briefly review the most relevant data, in the following paragraphs.

In 1977, Modlin et al.[57] studied 350 clinically confirmed cases of subacute sclerosing panencephalitis reported to a national registry. They reported that 292 patients had had measles and 58 had no history of measles. Forty of the latter 58 patients had received live attenuated measles virus vaccine. In patients with a history of natural infection, measles had occurred before 2 years of age in 46%. The pre-patent period in these children was 7 years. In contrast, there was no association between young age at vaccination and subacute sclerosing panencephalitis in the patients historically associated with measles vaccine, and subacute sclerosing panencephalitis occurred a mean of 3.3 years after vaccination. The risk of subacute sclerosing panencephalitis following natural measles was calculated to be 5.2 to 9.7 events per million cases and possibly 0.5 to 1.1 cases per million doses after vaccination.

It should be noted that the vaccine-associated risk reported by Modlin et al.[57] may be an artefact based upon the age at which the vaccine was given. Indeed, if it is assumed that subclinical or unrecognised measles occurred in the 40 'vaccinated children' in this study (e.g. modified measles in the presence of maternal antibodies), then the pre-patent period for the subacute sclerosing panencephalitis which developed in this group is identical to that observed following natural disease.

Dyken et al.[58] described 566 patients with subacute sclerosing panencephalitis including 68 patients in whom there was a history of vaccination alone (14.8%). This rate is actually lower than might be expected for healthy persons in the general population with detectable serum antibodies who deny a history of natural measles (i.e. patients who have experienced subclinical or unrecognised measles). The 103 patients who had been exposed to both wild-type measles and vaccine strain virus had the same pattern and severity of disease as the 265 with natural measles alone and the 68 who reported vaccination alone.

It is reassuring that only wild-type measles virus have been isolated from patients with subacute sclerosing panencephalitis.[59] It is also reassuring that not a single case of subacute sclerosing panencephalitis was reported in Canada in 1997, where there is a country-wide active surveillance system for subacute sclerosing panencephalitis (P. Duclos, unpublished observations). It nevertheless remains important to continue accumulating data and to multiply efforts to isolate and sequence measles strains isolated from patients with subacute sclerosing panencephalitis.

5.6 Transverse Myelitis

Similar to the argument for optic neuritis, the capacity of wild-type measles to initiate demyelinating disease, i.e. post-infectious encephalomyelitis, provides some biological plausibility for an association between vaccine strain measles and transverse myelitis. Given the limited number of cases, the Institute of Medicine committee considered the evidence inadequate to accept or reject a causal relationship for transverse myelitis despite the biological plausibility.[19] There have been no new case reports associating measles-containing vaccines with transverse myelitis since 1994.

5.7 Guillain Barré Syndrome

The Institute of Medicine report[19] acknowledged the biological plausibility for a causal relationship between measles vaccine and Guillain Barré syndrome, and noted that case reports, case series and uncontrolled, observational studies have been published in the literature. Although temporally related to immunisation, many of the published cases lack sufficient clinical details to preclude a definitive determination of causality. The committee concluded that the evidence was inadequate to accept or reject a causal relationship between measles vaccine and Guillain Barré syndrome.

Recently, da Silveira et al.[60] analysed 2296 cases of Guillain Barré syndrome that were reported to the Poliomyelitis Eradication Surveillance System of the Pan American Health Organization as cases of suspected poliomyelitis. These cases had occurred among 73 million children aged between 9 months and 15 years of age who had been targeted for immunisation in mass measles vaccination campaigns. Among these children, there was no excess in the number of cases of Guillain Barré syndrome compared with the number of expected cases in the 72 days following measles immunisation.

5.8 Thrombocytopenic Purpura

Evidence that wild-type measles virus is associated with thrombocytopenia provides biological plausibility to the idea that measles vaccine could also be associated with abnormalities in platelet number or function. In 1994, the Institute of Medicine concluded that the available evidence was sufficient to establish a causal relationship between MMR and thrombocytopenia but that it was inadequate to accept or reject a causal relationship between monovalent measles vaccines and thrombocytopenia.[19]

By linking vaccination records with computerised hospital admission records in 5 district health authorities, Farrington et al.[37] recently found a strong association between MMR vaccination and hospitalisation for immune thrombocytopenic purpura 15 to 35 days after vaccination. Two different mumps strains were used during the period of the study and there was no evidence of a mumps strain–specific effect. This is consistent with the view that immune thrombocytopenic purpura results largely from the other components of the vaccine. The estimated attributable risk was 1 in 29 000 doses of vaccine.

Further confirmation of this association comes from a retrospective review of thrombocytopenic purpura in France between 1984 and 1992[61] and a study of a series of thrombocytopenic purpura cases from the US Vaccine Adverse Events Reporting System[62] between 1990 to 1994 (n = 56). The French review identified 60 cases of thrombocytopenic purpura in patients who had received measles vaccine, giving an incidence of 0.17/100 000 doses of measles vaccine.[61] In the American series, thrombocytopenic purpura occurred in 3 children receiving a second dose of MMR; 1 case was a positive rechallenge.[62]

These data support a causal relationship only with MMR and not with the measles component itself. However, it may be prudent to check measles serostatus and to defer a second dose of a measles-containing vaccine if an episode of thrombocytopenic purpura or immune thrombocytopenic purpura occurred within 6 months of the first dose.[36]

5.9 Ulcerative Colitis and Crohn's Disease

Based upon a series of pathological and epidemiological studies, researchers in the UK and Sweden have recently suggested that Crohn's disease might be the late result of measles virus infection at a critical time during early childhood. Wild-type virus was implicated initially,[63,64] but an article by Thompson et al.[4] published in 1995 pointed an accusing finger at measles vaccines. The Thompson et al.[4] publication fuelled a prolonged and ongoing debate that, in our view, at times has escaped the field of science to enter the field of passion with letters and editorials fired back and forth.

It is hard to do justice to the entire sequence of events and publications. We will first present the evidence in favour of an association between measles and Crohn's disease and then summarise the evidence that weighs against such an association.

5.9.1 Evidence to Support an Association

Most of the work supporting an association between Crohn's disease and measles vaccine has been performed by Wakefield and colleagues of the Royal Free Hospital Inflammatory Bowel Disease Study Group. Using transmission electron microscopy, immunohistochemistry and *in situ* hybridisation,[63] as well as immunogold electron microscopy,[65,66] these authors have suggested that measles virus and subacute sclerosing panencephalitis–like pathology can be shown to be present in inflammatory bowel tissues affected by Crohn's disease.

Daszak et al.[66] noted that gold staining was significantly higher in granulomatous versus non-granulomatous areas of Crohn's disease tissue suggesting that the distribution of measles antigen was similar to that seen in subacute sclerosing panencephalitis. Subsequently, Miyamoto et al.[67] have reported the use of a monoclonal antibody directed against the measles M protein to detect immunoreactive cells in the tissues of 10 patients with Crohn's disease. No reactivity was present in 21 patients with other inflammatory bowel diseases. Knibbs et al.[68] have reported nuclear and cytoplasmic inclusions containing virus-like rows of tubular structures in intestinal endothelial cells and macrophages in 3 patients from a family with a history of Crohn's disease.

The first epidemiological study that showed a link between measles infection and Crohn's disease was published in 1994.[63] It compared the expected and observed month of birth in Swedish patients with Crohn's disease in relation to measles epidemics (1945 to 1954). The standardised incidence ratio was 1.46 (95% CI 0.83 to 2.21) for the development of Crohn's disease for births during the 3 months after the peak incidence of measles.[63]

A second paper suggested that measles vaccine may also play a part in the development not only of Crohn's disease but also of ulcerative colitis.[4] In this study, over 3000 individuals who participated in a 1964 measles vaccine trial in the UK were questioned about the subsequent development of inflammatory bowel disease (IBD). An increased risk of Crohn's disease and ulcerative colitis was found in vaccinated individuals compared with 11 407 slightly older unvaccinated control individuals participating in a child development study [RR 3.01 for Crohn's disease (95% CI 1.45 to 6.23) and 2.53 (95% CI 1.15 to 5.58) for ulcerative colitis].[4]

The third epidemiological paper supporting this association described the outcome of maternal measles infection in a Swedish cohort of 25 000 babies born from 1940 to 1949.[69] Three of the 4 children exposed to measles *in utero* subsequently developed Crohn's disease.

5.9.2 Evidence Refuting an Association

Three types of evidence weigh against the hypothesis that measles vaccine and measles virus causes Crohn's disease: biological, microbiological and epidemiological. Much of these data have been summarised elsewhere.[70]

Biological Evidence

The proponents of the hypothesis that Crohn's disease is caused by measles vaccine and measles virus make, in our view, an unsubstantiated parallel between Crohn's disease and subacute sclerosing panencephalitis and use this parallel extensively in their arguments of biological plausibility. However, the incidence of subacute sclerosing panencephalitis has declined dramatically since the introduction of measles vaccine while the incidence of Crohn's disease has increased. In our view, this simple observation strongly suggests a different pathogenesis of these 2 diseases.

Microbiological Evidence

The published reports cited in section 5.9.1 in support of the hypothesis[63,65-68] are subject to a large number of technical and methodological concerns.[70,71] In particular, in our view, the investigators at the Royal Free Hospital (Inflammatory Bowel Disease Study Group) have repeatedly chosen to use relatively subjective methods (e.g. *in situ* hybridisation, immunohistochemistry) to support their contention. It appears to us that there is also a systematic lack of detail in the description of both case and control material and data collection such that interpretation of the results is very difficult.

In 1 study, an independent group was unable to reproduce the findings of Wakefield et al.[63] using reagents provided by the Royal Free Hospital (Inflammatory Bowel Disease Study Group).[72] Several groups, including the investigators at the Royal Free Hospital (Inflammatory Bowel Disease Study Group), found no evidence of persistence of measles virus in Crohn's disease tissues when a more sophisticated and sensitive test [reverse transcriptase polymerase chain reaction (PCR)] was used.[73-76]

Haga et al.[73] used primers for measles, mumps and rubella viruses to screen biopsy material from 15 patients with Crohn's, 14 with ulcerative colitis, and 14 control individuals without IBD. No viral genomic sequences were found in any intestinal specimen.

More recently Afzal et al.[74] used an even more sensitive nested PCR protocol to look for measles virus nucleic acids in clinical specimens from 19 patients with IBD and 11 control participants. No specific signal was detected in the blood lymphocytes or colonoscopic biopsy specimens from these 30 patients.

Certainly, the most striking microbiological argument against the hypothesis comes from work by Iizuka et al.[75,76] Using the same monoclonal antibody that Wakefield and colleagues used in their immunohistochemical studies[63] (MAS 182r), Iizuka et al.[75] were able to confirm that intestinal tissue of Crohn's disease patients are indeed immunoreactive despite the absence of measles virus nucleic acids. These investigators then used MAS 182r to screen 1.5 million clones in a λgt11-expression library constructed from intestinal tissue surgically excised from a 38-year-old patient with Crohn's disease.[76] They identified and sequenced one MAS 182r positive clone which proved to be 99% homologous with an as yet undefined human gene. They then produced a monoclonal antibody (4F12) against this protein which co-localised with MAS 182r in double-labelled Crohn's intestinal biopsies. Although the authors correctly acknowledge the remote possibility that the antigen recognised by 4F12 and MAS 182r is a measles virus protein, it is far more likely that the previous immunochemical observations can be accounted for by antigen mimicry between measles virus and a host protein found in the intestinal tissue of Crohn's disease patients.

A number of serological studies also argue against the hypothesised association between Crohn's disease and measles. High serum and cerebrospinal fluid measles antibody titres are a characteristic of subacute sclerosing panencephalitis. In contrast, 2 studies have shown that measles virus–specific complement fixation titres are, if anything, lower in Crohn's disease patients than in control participants.[77,78] In one of these studies,[77] an IgM enzyme-linked immunosorbant assay (ELISA) also failed to demonstrate evidence of measles infection in the Crohn's group.

Although Balzola et al.[79] have reported high levels of measles–specific IgM antibodies in 78% of 36 patients with Crohn's disease and in 13 of 22 (59%) patients with ulcerative colitis compared with only 3 of 89 control individuals (3.3%), they used a highly subjective test (indirect immunoflu-

orescence) and did not indicate whether reading of the slides had been performed in a blinded manner. Critical clinical information about the study participants was also lacking, e.g. previous measles infection or immunisation status.

Epidemiological Evidence

The epidemiological studies performed by the Royal Free Hospital – Inflammatory Bowel Disease Study Group have serious methodological flaws.[4,63,69] The major weaknesses have been pointed out in a number of letters and editorials[80-88] and have been reviewed previously.[70] Of equal importance, several epidemiologically sound studies from a number of different groups have failed to identify an association between measles and Crohn's disease.

Nielsen et al.[89] examined the records of all possible cases of measles in pregnancy admitted to hospital in Copenhagen between 1915 to 1966. The children of 25 women who had had measles during pregnancy were identified and none were found to have developed Crohn's disease.

Hermon-Taylor et al.[90] compared the incidence of Crohn's disease with notifications of measles infection in England and Wales, including data collected after the introduction of measles vaccines. They found no association. Jones et al.[91] reported a case-control study of a large cohort of individuals exposed to viral infections during gestation, including 47 people exposed to measles *in utero*. Follow-up data on 88% found no individual with IBD among the index cases, but 2 patients with IBD among the control participants (1 of these patients had Crohn's disease).

A case-control study by Feeney et al.[92] compared measles vaccination histories in 140 patients with IBD (83 with Crohn's disease) with those of matched control individuals and found no association.[92-94]

In another study in the UK, a questionnaire was mailed to the 16 875 members of 2 associations of chronic IBD patients.[95] The birth-date distribution of patients with chronic IBD who were born between 1950 and 1958 was compared to the birth-date distribution of control individuals born in the same 8-year period with respect to 10 measles epidemics which were known to have occurred during this period. The authors found no evidence of an association between the development of Crohn's disease and exposure to a measles epidemic before the age of 1 year.

This study was similar in design to the Swedish study[64] but the results were very different and no association was found between chronic IBD and measles.

An international, cooperative, case-control study involving 499 patients with chronic IBD from 9 countries and 998 control patients, failed to identify any difference in IBD risk for either measles vaccination or measles infection (analysed until 6 and 10 years of age, respectively).[96] The main differences found in the study between patients with IBD and control participants were hereditary rather than environmental or infectious factors.[70,97]

Finally, in 1994, close to 7 million children in the UK received a combined measles-rubella vaccine in a massive catch-up campaign. To date, national data from hospital visits show no increase in new cases or exacerbation of existing cases of Crohn's disease following this campaign.[98]

Three reviews by independent groups concluded that the current scientific data do not permit a causal link to be drawn between the measles virus and chronic IBD and that the findings of Wakefield et al. were artefactual.[97]

In their comprehensive review, Lione and Scialli[99] concluded that things *'looked relatively bleak for the hypothetical association between measles virus and Crohn's disease, and even more so for a possible role for perinatal exposure to measles and Crohn's disease'*. They commented that *'The measles debate should remind us, however, that the scientific method ought to be an inherently sceptical process, with avoidance of too rapid acceptance of tantalising but unproven hypotheses'*.

It now appears to be most likely that ulcerative colitis and Crohn's disease are not caused by a specific, persistent infection but rather that luminal bacteria can sometimes induce chronic intestinal and systemic inflammation in genetically susceptible hosts.[100]

5.10 Autism

Recently, 2 case series were reported that suggested a link between immunisation with a measles-containing vaccine and autism.[5,101]

The study by Fudenberg[101] was included in the report of a pilot study of dialysable lymphocyte extract in infantile onset autism. Fudenberg studied 40 patients with infantile autism and reported that 15 of the 'true' autistic patients developed symptoms within a week after immunisation with MMR vaccine.

The second study by Wakefield et al.,[5] was a review of 12 children with chronic enterocolitis and regressive developmental disorders who were evaluated in a paediatric gastroenterology unit. The onset of behavioural symptoms was reportedly associated with MMR vaccination by the parents in 8 of the 12 children. Although the authors suggest that there is a potential relationship to the vaccine, they admit that their findings do not constitute a proof of causality.[5]

Both papers rest on the hypothesis that MMR vaccination leads to a nonspecific gut injury permitting the absorption of nonpermeable peptides which in turn cause serious developmental disorders.

These 2 reports have many limitations. Although the first attracted surprisingly little attention and generated little controversy, the second resulted in a flurry of letters to the editor severely criticising the article and its implications.

The report by Fudenberg is noncomparative and anecdotal.[101] Unsubstantiated claims, as well as gross inaccuracies, for example referring to hepatitis B vaccine as a live vaccine, cast considerable doubt on the validity of the entire report.

The report by Wakefield et al.[5] is also noncomparative and anecdotal. As pointed out by Chen and deStefano[102] in the accompanying editorial, each year over 600 000 British children receive MMR in their second year, an age when autism typically manifests. Chance alone dictates that many cases of autism will appear shortly after vaccination.[102] Chen and DeStefano[102] also questioned the apparent paradox that neurological symptoms preceded bowel symptoms in most of the children included in the study by Wakefield et al.[5] while the measles-autism hypothesis would predict the opposite sequence of events. The nonspecific colitis and lymphoid hyperplasia implicated by Wakefield et al.[5] in the pathogenesis of autism is common[103-105] and is widely believed to be benign.[106]

Although 4 out of 12 of the children included in the study by Wakefield et al.[5] were said to have abnormally low Ig levels, the authors used adult reference ranges. According to Gilat et al.[96] if appropriate paediatric ranges are applied, only 1 child had slightly low IgA levels.

Finally, in our view the very 'precision' of the vaccination-autism interval in the study by Wakefield et al.[5] makes this study suspect. The onset of autism is almost always insidious, progressing over months rather than starting on a particular day. In 5 out of 8 children, the onset of the so-called autism-bowel syndrome is precisely described (after 1 to 14 days).[107]

National data from the UK and Sweden show no relationship between the rate of autism and the introduction of MMR vaccine.[108] Wing[109] reviewed 16 studies in Europe, North America and Japan and found no evidence of an increase in autism with increasing use of measles-containing vaccines. Two large European data sets have been examined by Fombonne[110] to look for coincidence of autism and IBD without success.

A small study by Payne and Mason[111] in the UK, looked at vaccination coverage in autistic children and found an MMR coverage rate of 88.9 and 95.3% for autistic and nonautistic children, respectively. Finally, in Finland, out of 3 million children immunised with MMR vaccine and prospectively followed up during a 2- to 3-week period after immunisation, Peltola et al.[112] identified 31 children who had developed gastrointestinal symptoms or signs lasting 24 hours or more at any time after receiving the vaccine. These children were followed up with an interval between reported event and health check that varied from 16 months to 15 years and 1 month. None of them had developed an autistic-spectrum disorder. Although acute encephalitis from any cause can occasionally lead to autistic features, this association has not been re-

ported for post-infectious encephalomyelitis induced either by wild-type measles or (possibly) measles vaccination.

At the request of the Chief Medical Officer, the UK Medical Research Council convened a group of national and international experts in early 1998 to consider the postulated relationship between measles, MMR vaccines, Crohn's Disease and Autistic Spectrum Disorder. The group included experts in virology, epidemiology, immunology, paediatrics, child psychiatry, autism, gastroenterology and Crohn's Disease. The group reviewed the work of the Royal Free Hospital – Inflammatory Bowel Disease Study Group in detail. The group came to the conclusion that there is no evidence for a link between measles, measles vaccine or MMR immunisation and either Crohn's Disease or autism.[113]

5.11 Type 1 Diabetes Mellitus (Insulin-Dependent Diabetes Mellitus)

There is no demonstrated biologically plausible reason to suggest a causal relationship between monovalent measles vaccine and type 1 diabetes mellitus (insulin-dependent diabetes mellitus). Indeed, the available data demonstrate a decreased RR for type 1 diabetes mellitus in individuals who have received measles vaccination.[114] In 1994, the Institute of Medicine concluded that the evidence was inadequate to accept or reject a causal relationship between measles or mumps vaccine and type 1 diabetes mellitus.[19]

5.12 Death As a Consequence of Vaccine-Strain Viral Infection in Immunocompromised Patients

Measles infection in the immunocompromised patient can be prolonged, severe, and is frequently fatal. Infection of persons with defective cell-mediated immunity may occur in the absence of rash. Two especially severe complications of measles in the immunocompromised host are inclusion body encephalitis[115,116] and a giant cell pneumonia (Hecht pneumonia).[117,118]

Inclusion body encephalitis is a progressive infection of the brain in patients unable to mount an effective cellular immune response. Inclusion body encephalitis typically occurs 1 to 6 months after measles and is distinct from post-infectious encephalomyelitis and subacute sclerosing panencephalitis; its latent period is intermediate between these 2 conditions. The incidence of inclusion body encephalitis in severely immunocompromised persons is approximately 1 per 10 measles cases.

Several measles deaths have been reported in immunocompromised children following the administration of live attenuated vaccine. Using RNA-templated sequencing, vaccine-strain measles virus has been implicated as the cause of death in 3 immunocompromised children with inclusion body encephalitis[19,119] to date.

Giant cell pneumonia is a potential cause of severe morbidity and mortality in immunocompromised individuals exposed to measles vaccine. For example, a case of pneumonia progressing over 12 months has recently been reported in a 21-year-old man with AIDS following administration of a second dose of live attenuated vaccine.[120,121] Measles virus was repeatedly isolated from lung biopsies and sequence data showed that the causative organism was closely related to the vaccine-strain virus.[120,121]

This case reinforced concerns over the safety of routine measles reimmunisation of patients with advanced HIV infection and resulted in a change in the recommendations of the US Advisory Committee on Immunisation Practices.[122] The administration of measles vaccine or MMR is specifically contraindicated in any individual whose immune system is seriously impaired as a result of disease or therapy. Nevertheless, most HIV-positive children are able to receive the first dose of MMR at the age of 6 months as recommended by the WHO or at 12 to 15 months of age without undue risk.[123]. In developing countries where extensive diagnostic services are not routinely available, the WHO also recommends giving such children a second dose at 9 months of age, or as soon as possible thereafter.

Consultation with an expert is strongly advised if measles vaccination is considered in an individual with any significant degree of immunodeficiency.[124,125] To our knowledge, with the excep-

tion of a number of deaths unfortunately resulting from programmatic mistakes,[24] no immunocompetent person has ever died as a result of receiving a properly handled standard titre measles-containing vaccine.

6. Risks and Benefits of Measles Immunisation

Natural measles is a serious disease with frequent complications whereas vaccination with live attenuated virus is remarkably benign (see table I). In healthy individuals, the only serious complications from measles immunisation are anaphylaxis, thrombocytopenic purpura and, possibly, post-infectious encephalomyelitis. Anaphylaxis and thrombocytopenic purpura are associated with no long term consequences if they are properly managed and thrombocytopenic purpura and post-infectious encephalomyelitis are at least 1 to 2 orders of magnitude more common following natural disease than after vaccination. Only anaphylaxis is unique to the vaccine and it may be possible to reduce this risk now that the most likely allergen has been identified.[44]

The balance of risks and benefits for any health intervention can be viewed from 2 perspectives: that of the population and that of the individual. Health professionals performing vaccinations and vaccine policy-makers must learn to recognise these 2 perspectives and to communicate benefit-risk information effectively at both levels.

The factors which enter into a determination of risks and benefits are myriad and include the immune status of the individual, age, medical condition and state of control of the target organism, the risk of importation, and the level of 'herd' immunity, to name a few. In Canada, which is a country with a fairly long history of vaccination, it may appear to the general population that measles has essentially disappeared. Indeed, with only 200 to 600 cases a year, the incidence of measles in the last few nonepidemic years has been around 1.5 per 100 000 person-years. This risk is not evenly distributed (e.g. by age, geographical location) or equally shared by all Canadians. In fact, with a 97% vaccine coverage rate, the total risk of natural measles is highly concentrated in the relatively small, unvaccinated population.

Table I. Risk of complications from natural measles infection compared to known risks of vaccination with a live attenuated virus in immunocompetent individuals

Complication	Risk after natural measles[a]	Risk after vaccination[b]
Otitis media	7-9%	0
Pneumonia	1-6%	0
Diarrhoea	6%	0
Post-infectious encephalomyelitis	0.5-1 per 1000	1 per 1 000 000
SSPE	1 per 100 000	0
Anaphylaxis	0	1 per 100,000-1,000,000
Thrombocytopenia	–[c]	1 per 30 000[d]
Death	0.1-1 per 1000 (up to 5-15% in developing countries)[7]	0

a Risks after natural measles are calculated in terms of events per number of cases.

b Risks after vaccination are calculated in terms of events per number of doses.

c Although there have been several reports of thrombocytopenia occurring after measles including bleeding, the risk has not been properly quantified.

d This risk has been reported after MMR vaccination and cannot be only attributed to the measles component.

MMR = measles, mumps and rubella; **SSPE** = subacute sclerosing panencephalitis.

Given the contagiousness of measles and the inevitability of importation until measles is eradicated worldwide, we estimate that the incidence of natural infection in an unvaccinated Canadian under 20 years of age approaches 1 per 1000 persons per year or 1 per 50 persons for the first 20 years of life. This risk obviously increases with certain occupations (e.g. school teacher) and with foreign travel and may approach 1 per 20 persons over a lifetime. If this fairly substantial lifetime risk is used to calculate the known risks for major measles sequelae, what remains is a risk of 1 per 60 000 persons for measles-related death, 1 per 20 000 persons for post-infectious encephalomyelitis, 1 per 2 000 000 persons for subacute sclerosing panencephalitis, 1 per 400 persons for pneumonia, and 1 per 60 persons for measles-associated hospitalisation. These numbers stand in sharp con-

trast to the estimated lifetime risk for the most serious vaccine-associated sequelae: anaphylaxis (<1 per 1 000 000 vaccine doses administered); post-infectious encephalomyelitis (possibly <1 per 1 000 000 vaccine doses administered); and transient thrombocytopenia (1 per 29 000 vaccine doses administered).

Although minor reactions to measles-containing vaccines are relatively more common, cost-benefit studies that take into account the occurrence of these reactions have shown that measles immunisation programmes are highly beneficial and cost saving and that even a catch-up campaign and implementation of a 2-dose programme could be cost saving in countries like Canada.[126]

These numbers suggest that the balance of risks to benefits is highly in favour of vaccination in countries with a low incidence of natural infection. In countries where measles remains endemic and measles mortality is high, the benefits of immunisation are enormous.

We believe that only when the world is nearing global measles elimination might the individual risks of vaccination compare unfavourably with the risks of remaining unvaccinated. Although the benefit-risk balance will still strongly favour the vaccine at a population level, considering the societal health and economic benefits that will be achieved with disease eradication, a prolonged period of near-elimination might necessitate the search for safer measles vaccines. The faster the world commits to and moves towards global eradication, the more likely that eradication can be accomplished with the currently available vaccines.

With respect to immunocompromised persons, the risk of complications and death from measles vaccine has to be compared with even greater risk from natural measles infection. In light of the global AIDS epidemic, it seems important to favour administration of measles immunisation at the youngest possible age when children are unlikely to have developed serious immune deficiencies. In children who present with major immune deficiencies, the vaccine should not be administered. In the long run, these children will hopefully benefit from the global drive towards measles elimination.

For persons receiving a second dose of measles vaccine, it is likely that 9 out of 10 will already be fully protected by the first dose leading to immediate and complete neutralisation of the vaccine virus. Therefore, it is reasonable to assume that the risk of events will be decreased by a factor of 10 with the exception of allergic reactions. Likewise, there is no reason to believe that persons receiving more than 2 doses would be at higher risk for adverse reactions.

7. Conclusion and Discussion

It is inevitable that vaccine safety concerns will increase in prominence as the incidence of a vaccine-preventable disease falls to negligible levels and vaccine coverage approaches 100%. On the one hand, it is the rarely acknowledged, vaccine-induced absence of severe morbidity and mortality from natural disease that allows the public, the lay media, and some investigators to focus on rare vaccne-associated adverse events and spurious claims of associations.

On the other hand, both true and false events increase as a function of vaccine usage: true associations because there is yet no vaccine that is 100% safe in 100% of the population and; false associations because the universal use of any vaccine will inevitably mean that vaccinations are administered prior to the occurrence of other unfortunate events. As a result, we were not surprised that the most recent allegations against measles vaccines arose and found fertile ground in England after the mass catch-up campaign had been implemented in 1994, bringing measles incidence to very low levels. These allegations have caused considerable parental concern and decreased measles vaccine acceptance rates despite the lack of evidence of a causal relationship and intense and largely negative evaluations of the data supporting the allegations.[6,24,127]

Those charged with national vaccination programmes throughout the world have a sense of ‘déja vu’ as they recall the negative publicity which decreased pertussis vaccine uptake in the 1970s and resulted in major outbreaks of whooping cough and hundreds of tragically unnecessary deaths.[128]

Clearly, the wide dissemination of spurious associations can snowball into societal tragedies.

Vaccine-associated adverse events occur and rare events occasionally lead to serious and permanent harm. Vaccine-associated paralytic polio associated with oral polio vaccine is an excellent example of an adverse effect which can even harm members of a vaccinee's family and close contacts. Furthermore, it is unlikely that we have identified all of the potential adverse events associated with the currently available vaccines. However, given the surveillance efforts initiated in the last decade, it is likely that only extremely rare adverse events may possibly have been missed.

How do we reconcile these observations with the intensely critical response[129-131] to the reports of an association between measles-containing vaccines and Crohn's disease and autism? Some have gone so far as to suggest that research publications should carry health warnings like cigarettes.[132] The principal authors of these reports and the editor of the journal in which some of the most controversial findings have been published have tried to explain the debate in terms of the different approaches taken by public health authorities versus clinicians. Concerns have also been raised about fairness to the principal author.[133-135] After all, we are often inclined to blame the messenger.

We believe that these arguments are diversionary driving a wedge between public health and clinical medicine and could be terribly damaging to the cause of broad vaccine acceptance and coverage. We suggest that the real issue is one of good science versus bad science which would apply equally to the areas of public health and clinical medicine. We believe that several of the reports alleging an association between Crohn's and autism and measles vaccine are in the public domain through failure of the peer review process.

While disruptive, the Crohn's/autism debate has been useful at one level. Despite the failures of the peer review process, the larger scientific community has responded with alacrity to debunk the bad science. The rapidity of this response, including the convening of an independent review panel in the UK, has demonstrated that those charged with vaccination programmes have learned from previous mistakes. The reaction to a newly published vaccine-associated adverse event has to be rapid for several reasons. First, the reported association may be true which would force an urgent reevaluation of programmes and policies regarding the implicated vaccine. However, if the reported association is false, immediate action is necessary to deliver a credible counter-message to minimise the negative impact on vaccination programmes. Of course, practitioners of both public health and clinical medicine would be best served if spurious allegations were deflected before they hit the news stand. The response to each unfounded allegation consumes energy and resources which could be better used to address real issues of vaccine safety.

The credibility and success of vaccination programmes worldwide depend on the safety of each and every vaccine. New vaccines are entering the market at an unprecedented rate and established vaccines are seeing ever wider applications. These factors make the monitoring of vaccine safety one of the most important issues in healthcare today. The need for computerised immunisation registries and international links to monitor vaccine safety is now acute. Those charged with monitoring vaccine safety must expand and refine surveillance activities and make full use of all the modern scientific tools available to this end (e.g. molecular epidemiology to distinguish between vaccine and wild-type strains). The global elimination of smallpox was a major accomplishment for mankind. The elimination of polio and measles is now within our grasp. Our ability to credibly monitor vaccine safety is critical to these eradication efforts.

During a 30-year period of worldwide use, measles immunisation has proven to be one of the safest and most successful health interventions in the history of mankind. The risks and benefits of measles immunisation are highly in favour of administering the vaccine even in countries with a very low incidence of measles and high rates of measles vaccine coverage.

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