Research letters

No evidence for measles, mumps, and rubella vaccine-associated inflammatory bowel disease or autism in a 14-year prospective study

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Concern[1] of potential loss of confidence in measles, mumps, and rubella (MMR) vaccine has been raised by a recent paper[2] that suggested a causal association between this vaccine (or another environmental trigger) and a new syndrome of chronic inflammatory bowel disease and autism. Characteristically, all children described developed intestinal symptoms within days or soon after vaccination.

The National Board of Health and National Public Health Institute launched a long-term vaccination project in 1982, which aimed at the elimination of MMR diseases from Finland.[3] All children are vaccinated twice, at age 14–18 months and 6 years; further vaccinations are carried out among recruits of the defence forces and in some schools of nursing. Only one type of live-virus vaccine (MMR or Virivac [Merck, West Point, PA, USA]) consisting of the more attenuated Enders Edmonston, Jeryl Lynn, and Wistar RA 27/3 strains for measles, mumps, and rubella, respectively, has been used since beginning of the project. Adverse events in temporal relation to MMR vaccine were reported prospectively to the Institute. A form was filled and posted to us, followed by another form with further information 2–3 weeks later. We traced those vaccinees who developed gastrointestinal symptoms or signs lasting 24 h or more at any time after MMR vaccination (apart from within the first hour). We checked hospital or health centre records or interviewed the local public-health nurses.

By the end of 1996, about three million vaccine doses had been delivered by the Institute. 31 children developed gastrointestinal symptoms after vaccination (table); all except one after the first vaccine dose. *Haemophilus influenzae* type b conjugate vaccine was given concomitantly in four cases. 20 patients were admitted to hospital. Antibiotics were given in 11 cases, symptomatic relief in nine, and intravenous γ-globulin was given to one child with Guillain Barré syndrome.

The time between the reported event and our check on their health varied from 1 year and 4 months to 15 years and 1 month. The mean interval was 9 years 3 months, the median being 10 years and 8 months.

Diarrhoea, frequently with vomiting, was the most common symptom (55%, n=17), followed by gingivostomatitis (23%, n=7), vomiting only (16%, n=5), and abdominal pains (n=2). The time from MMR vaccine to onset of symptoms varied from 20 h to 15 days. Duration of symptoms was not always stated or recalled by nurses, but subsidence within a week was usual, except in a 1-year-old boy (patient 23) whose diarrhoea lasted for 6 weeks. The child recovered and was healthy when checked almost 6 years later. Most symptoms and signs of the central nervous system were those one would expect in conjunction with acute gastrointestinal disease: five (16%) children had febrile seizures and two had headache. One child developed ataxia

Child	Sex	Vaccination		Interval from vaccination to intestinal symptoms	Symptoms other than intestinal	Duration of intestinal symptoms	Admitted to hospital	Time elapsed until check-up
		Year	Age					
1	M	1982	6 yr 11 mo	≈1 week	Fever, seizure, pneumonia	<1 week	Yes	11 yr 3 mo
2	F	1982	1 yr 9 mo	5 days	Fever, tonsillitis	3 days	Yes	9 yr
3	F	1982	6 yr 11 mo	1 day	Fever, headache	≈4 days	No	7 yr
4	M	1982	1 yr 6 mo	2 days	Fever, respiratory	≈1 week	Yes	5 yr 9 mo
5	F	1983	1 yr 5 mo	9 days	. .	Not stated	Yes	15 yr 1 mo
6	F	1983	1 yr 2 mo	9 days	Fever, seizure	≈2 days	Yes	15 yr 1 mo
7	M	1983	6 yr 11 mo	13 days	Fever	5 days	Yes	15 yr 1 mo
8	F	1983	6 yr 5 mo	10 days	Fever, otitis, headache	Not stated	No	14 yr 11 mo
9	M	1983	1 yr 6 mo	11 days	Fever, rash, pneumonia	Not stated	Yes	14 yr 9 mo
10	M	1983	1 yr 3 mo	13 days	Fever, seizure, rash	5 days	Yes	14 yr 8 mo
11	F	1983	1 yr 3 mo	4 days	Fever, rash	Not stated	Yes	14 yr 6 mo
12	F	1983	1 yr 3 mo	4 days	Fever, seizure, otitis	1 week	Yes	14 yr 5 mo
13	M	1983	2 yr 7 mo	8 days	Fever, lymphadenopathy	Not stated	No	13 yr 8 mo
14	F	1983	4 yr 6 mo	6 days	Fever, probable pneumonia	5 days	Yes	13 yr 7 mo
15	F	1984	3 yr 11 mo	20 h	Fever, rash	Not stated	Yes	14 yr
16	F	1984	1 yr 3 mo	3 days	Fever, seizure	1 week	Yes	13 yr 9 mo
17	M	1984	1 yr 7 mo	≈2 weeks	. .	Not stated	No	4 yr
18	M	1985	1 yr 4 mo	3 days	Fever, tonsillitis	Not stated	Yes	11 yr
19	M	1985	1 yr 9 mo	5 days	Fever, lymphadenopathy	Not stated	Yes	7 yr 11 mo
20	F	1986	6 yr 10 mo	3 days	Fever, pneumonia, otitis	3 days	Yes	11 yr 5 mo
21	M	1987	1 yr 7 mo	9 days	Fever, rash, conjunctivitis, otitis	≈1 week	No	10 yr 8 mo
22	F	1989	2 yr 2 mo	4 days	Fever, respiratory	2 days	Yes	2 yr 10 mo
23	M	1991	1 yr 5 mo	7 days	Fever, rash, probable orchitis	6 weeks	No	5 yr 7 mo
24	F	1992	13 yr	3 days	Fever, urticaria, conjunctivitis	≈2 days	No	6 yr 1 mo
25	F	1993	1 yr 2 mo	15 days	Urticaria	≈2 days	Yes	4 yr 7 mo
26	M	1993	1 yr 5 mo	11 days	Fever, rash	6 days	No	4 yr 7 mo
27	M	1994	1 yr 9 mo	11 days	Fever, rash	≈2 days	No	3 yr 8 mo
28	F	1995	1 yr 5 mo	5 days	Fever, ataxia	4 days	Yes	2 yr 7 mo
29	M	1995	1 yr 6 mo	13 days	Fever, urticaria	≈2 days	No	1 yr 7 mo
30	F	1996	1 yr 7 mo	Not stated	Fever, rash	Not stated	Not stated	1 yr 9 mo
31	M	1996	1 yr 7 mo	11 days	Fever, Guillain Barré	5 days	Yes	1 yr 4 mo

Characteristics of patients with gastrointestinal and other symptoms after MMR vaccination

which subsided quickly. No child developed autistic-spectrum disorder. Hyperornithaemic gyrate atrophy, an autosomal recessive disease, was diagnosed in one girl (patient 14) 8 years after vaccination. A boy developed *H influenzae* meningitis, and a girl meningococcal meningitis 1 day and 7 days after vaccination, respectively.

It is noteworthy that, besides gastrointestinal complaints, many children had similar symptoms and signs (fever, rash, seizure) as those in London.[2] Presumably, some patients with symptoms or signs not far from those listed in the table were not reported to us. We do not deem this shortcoming to be of a major concern because illness in all our 31 patients was mild, and probably sometimes caused by concomitant infection.[4]

Over a decade's effort to detect all severe adverse events associated with MMR vaccine could find no data supporting the hypothesis that it would cause pervasive developmental disorder or inflammatory bowel disease.

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1 Lee JW, Melgaard B, Clements CJ, et al. Autism, inflammatory bowel disease, and MMR vaccine. *Lancet* 1998; **351:** 905–09.
2 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; **351:** 637–41.
3 Peltola H, Heinonen OP, Valle M, et al. The elimination of indigenous measles, mumps, and rubella from Finland by a 12-year, two-dose vaccination program. *N Engl J Med* 1994; **331:** 1397–402.
4 Tait DR, Ward KN, Brown DWG, Miller E. Measles and rubella misdiagnosed in infants as exanthem subitrum (roseola infantum). *BMJ* 1996; **312:** 101–02.

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Severe premature coronary artery disease with protease inhibitors

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Until recently, the prognosis for people with AIDS was so poor that concerns about other long-term health problems seemed irrelevant. The introduction of antiretroviral treatment with protease inhibitors has had a profound impact on mortality from AIDS.[1] After two young AIDS patients on protease inhibitors under our care developed coronary artery disease, we examined lipid abnormalities among HIV-1-infected people receiving protease inhibitors and designed an intervention based on the National Cholesterol Education Program (NCEP) guidelines.[2]

A 26-year-old HIV-1-infected man (CD4 T cell count <10 cells/μL) was admitted with angina. He had a history of cigarette smoking and occasional cocaine use (none recently). The plasma HIV-1-RNA level was more than 1 000 000 copies/mL, so 4 weeks before admission he was started on directly-observed ritonavir, saquinavir, lamivudine, and stavudine. Coronary angiography showed a large occlusive thrombus within the right coronary artery.

A 37-year old HIV-1-infected man presented with angina after shovelling snow. His lowest CD4 T-cell count was 14 cells/μL with a peak plasma HIV-1 RNA level of 685 000 copies/mL. He had developed cytomegalovirus retinitis and diabetes mellitus before starting protease inhibitors at age 35. He had a family history of heart disease but no history of cigarette smoking. His cholesterol concentration increased from 4·28 mmol/L before starting indinavir to 8·46 mmol/L 5 months later. 7 months before presentation his fasting cholesterol was 12·3 mmol/L, high-density cholesterol (HDL) 0·46 mmol/L, and triglycerides 22·14 mmol/L, while his plasma HIV RNA level was <500 copies/μL. He developed a right cervical region fat pad. He was taking gemibrozil 600 mg orally twice daily, aspirin, indinavir, zidovudine, and lamivudine. Coronary arteriography revealed occlusion of the left anterior descending artery and severe atherosclerosis involving the right coronary artery.

A review of 124 patients on protease inhibitors in our HIV clinic identified 41 (33%) with raised lipid concentrations who were referred for NCEP intervention. For 15 patients (mean fasting lipids-cholesterol 6·35 mmol/L; triglycerides 3·6 mmol/L), a diet exercise programme was instituted. 26 patients (mean fasting lipids-cholesterol 8·98 mmol/L; mean triglycerides 19·2 mmol/L) were referred for drug treatment (gemfibrozil for 3 months then atorvastatin).

Peripheral lipodystrophy has been reported in patients receiving protease inhibitors.[3,4] In one study, metabolic abnormalities (higher triglyceride, cholesterol, insulin, and C-peptide levels, and insulin resistance scores) were described in 72 (64%) of 116 patients after a mean 10 months on treatment.[5] Clinicians need to be aware of the potential for accelerated atherosclerosis in patients treated with protease inhibitors. For now, we obtain a fasting lipid profile before and then 3–6 months after the start of protease inhibitor therapy and then use NCEP guidelines to treat abnormalities identified.

1 Cameron DW, Heath-Chiozzi M, Danner S, et al. Randomized placebo-controlled trial of ritonavir in advanced HIV-1 disease. *Lancet* 1998; **351:** –49.
2 National Institutes of Health. Cholesterol lowering in the patient with coronary artery disease: physician monograph-national cholesterol education program. September 1997 (NIH Publication 97-3794).
3 Mann M, Piazza-Hepp T, Koller E, Gibert C. Abnormal fat distribution in AIDS patients following protease inhibitor therapy. FDA summary. In: Programs and Abstracts of the 5th National Conference on Retroviruses and Opportunistic Infections; Chicago, Illinois, Feb 1–5, 1998 (abstr 412).
4 Miller K, Jones E, Yanovsky J, Shankar R, Feuerstein I, Falloon J. Visceral abdominal-fat associated with use of indinavir. *Lancet* 1998; **351:** 871–75.
5 Carr A, Samaras K, Burton S, Freund, J, Chisholm DJ, Cooper DA. A syndrome of peripheral lipodystrophy and insulin resistance due to HIV protease inhibitors. In: Programs and Abstracts of the 5th National Conference on Retroviruses and Opportunistic Infections; Chicago, Illinois: Feb 1–5, 1998 (abstr 410).

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Hormone-receptor status of breast cancer in Papua New Guinea

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The survival of women with breast cancer varies with racial background and geographical location. Whilst black women have a higher mortality than white women, the causes of racial difference in breast tumour biology are unknown.[1] The well-known association between oestrogen (ER) and progesterone (PR) receptor status and both response to tamoxifen treatment and prognosis has prompted several