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Vaccination and Risk for Developing Inflammatory Bowel Disease: A Meta-Analysis of Case–Control and Cohort Studies

Guillaume Pineton de Chambrun,^{*,‡,§,k} Luc Dauchet,^{§,¶} Corinne Gower-Rousseau,^{*,‡,§} Antoine Cortot,^{*,‡,§} Jean-Frédéric Colombel,[#] and Laurent Peyrin-Biroulet^{§,**}

^{*}Gastroenterology and Hepatology Department, Lille University Hospital, Lille, France, [¶]Epidemiological Department, Lille University Hospital, Lille, France; [‡]Lille Inflammation Research International Center LIRIC-UMR 995 Inserm, Université Lille 2, CHRU de Lille, Equipe IBD and Environmental Factors: Epidemiology and Functional Analyses, Lille University, Lille, France; [§]Public Health, Epidemiology and Economic Health, Registre Epimad, Maison Régionale de la Recherche Clinique, Centre Hospitalier Universitaire Régional, Lille Cedex, France; ^kGastroenterology and Hepatology Department, Montpellier University Hospital, Montpellier, France; [#]Department of Gastroenterology, Icahn Medical School of Medicine at Mount Sinai, New York, New York; ^{**}Inserm U954 and Department of Gastroenterology, Université de Lorraine, Nancy les Vandoeuvre, France

This article has an accompanying continuing medical education activity on page e130. Learning Objective—Upon completion of this activity, successful learners will be able to discuss the implication of vaccination and environmental factors in the development of inflammatory bowel disease.

BACKGROUND & AIMS: Environmental factors may play a key role in the pathogenesis of inflammatory bowel disease (IBD). Whether vaccination is associated causally with IBD is controversial. We performed a meta-analysis of case–control and cohort studies on the association between vaccination and the risk for IBD.

METHODS: Studies and abstracts investigating the relationship between vaccination and subsequent risk for developing IBD were reviewed. Childhood or adult immunizations with any vaccine type, at any dose, and with any vaccine schedule were used as inclusion criteria.

RESULTS: Eleven studies were included in the systematic review and meta-analysis: 8 case–control studies and 3 cohort studies. Studied vaccines were bacille Calmette–Guérin, vaccines against diphtheria, tetanus, smallpox, poliomyelitis, pertussis, H1N1, measles, rubella, mumps, and the combined measles, mumps, and rubella vaccine. Only a few details about vaccine type or route of administration were found in studies. Overall, there was no association between childhood immunization and risk for developing IBD: bacille Calmette–Guérin, relative risk (RR) of 1.04 (95% confidence interval [CI], 0.78–1.38), diphtheria, RR of 1.24 (95% CI, 0.80–1.94), tetanus, RR of 1.27 (95% CI, 0.77–2.08), smallpox, RR of 1.08 (95% CI, 0.70–1.67), poliomyelitis, RR of 1.79 (95% CI, 0.88–3.66), an measles containing vaccines, RR of 1.33 (95% CI, 0.31–5.80) in cohort studies, and RR of 0.85 (95% CI, 0.60–1.20) in case–control studies. Subgroup analysis for Crohn's disease (CD) and ulcerative colitis (UC) found an association between the poliomyelitis vaccine and risk for developing CD (RR, 2.28; 95% CI, 1.12–4.63) or UC (RR, 3.48; 95% CI, 1.2–9.71). The RR of developing IBD after H1N1 vaccination was 1.13 (95% CI, 0.97–1.32).

CONCLUSIONS: Results of this meta-analysis show no evidence supporting an association between childhood immunization or H1N1 vaccination in adults and risk of developing IBD. The association between the poliomyelitis vaccine and the risk for CD or UC should be analyzed with caution because of study heterogeneity.

Keywords: Crohn's Disease; Ulcerative Colitis; Poliomyelitis; BCG; Vaccine; Childhood.

The etiology of inflammatory bowel diseases (IBDs) including Crohn's disease (CD) and ulcerative colitis (UC) remains unknown. The pathogenesis of IBD is thought to involve an altered immune response against gut microflora in genetically predisposed individuals, leading to mucosal inflammation and ulcerations.^{1,2} Currently, more than 100 susceptibility genes for CD and UC have been identified by a

Abbreviations used in this paper: BCG, bacille Calmette–Guérin; CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; IPV, injected inactivated vaccine; MMR, measles, mumps, rubella; OR, odds ratio; OPV, oral live vaccine; RR, relative risk; UC, ulcerative colitis.

genome-wide association scan study.³ Although genetic influence may play an important role in the development of IBD, several observations plead for equal implication of environmental exposure.^{4–6} The lack of complete penetrance of UC and CD among monozygotic twins and the limited familial occurrence of IBD (5%–10%) indicates that environmental factors play a role in the development of these disorders.^{7,8} Many environmental factors have been proposed as etiologic factors of CD or UC.^{8–10}

There is accumulating evidence that events early in life may have long-term effects on health and disease.^{8,11} In the same way, it has been suggested that attenuated live measles virus vaccine might lead to IBD.¹² The first report on the risk of developing IBD after a measles vaccination in leads to international controversy and suspicion about vaccination safety. Since then, several population-based, case–control and cohort studies have investigated the potential link between childhood immunization and IBD with conflicting results.^{11–21} Different types of vaccines were studied such as poliomyelitis, measles, rubella, mumps, smallpox, pertussis, tetanus, diphtheria, and bacille Calmette–Guérin (BCG).

An attractive theory is that vaccination, which leads to a decrease in the prevalence of early childhood infections, may favor immunologic diseases.²² A direct effect of viral or bacterial components included in vaccines on the immune system also may be implicated.²³ Finally, adjuvant contained in many vaccines, such as aluminum, could be at risk of overstimulating the immune system, leading to dysregulated inflammatory response.^{10,24} Overall, whether vaccination is associated causally with IBD remains controversial.

The aim of this study therefore was to perform a systematic review and meta-analysis of case–control and cohort studies on the association between vaccination and the risk of developing IBD.

Methods

Search Strategy and Study Selection

A systematic review and meta-analysis was conducted in accordance with guidelines for systematic reviews and meta-analyses published previously.²⁵ A computerized search of the medical English and non-English literature was conducted using MEDLINE (1970 to June 2014), EMBASE, and the Cochrane central register of controlled trials. Studies and abstracts investigating the relationship between vaccination and subsequent risk for the development of IBD were reviewed. Only randomized controlled trials, controlled clinical trials, cohort studies, and case–control studies investigating the risk for IBD after vaccination were eligible for inclusion. Childhood or adult immunizations with any vaccine type, at any dose, and with any vaccine schedule were used

as inclusion criteria. Potentially eligible studies were identified via a literature search using the terms ulcerative colitis, Crohn's disease, inflammatory bowel disease, colitis, or ileitis. These were combined using the set operator AND with studies identified with the following terms: vaccine, vaccination, immunization, smallpox, poliomyelitis, tetanus, diphtheria, pertussis, mumps, rubella, measles, measles, mumps, rubella (MMR) vaccine, BCG, or influenza vaccine. Abstracts of the articles identified by the initial search were evaluated by the lead investigator for appropriateness to the study question, and all potentially relevant articles were obtained and evaluated in detail. We searched the bibliographies of all relevant articles obtained and any published reviews for additional studies. Abstract books of conference proceedings from major congresses in gastroenterology, Digestive Diseases Week, United European Gastroenterology Week, and the European Crohn's and Colitis Organisation between 2002 and 2013 were hand-searched to identify potentially eligible studies published only in abstract form. Articles were assessed independently by 2 investigators using predesigned eligibility forms, according to the predefined eligibility criteria. Any disagreements between investigators were resolved by discussion.

Outcome Assessment

The outcome measures were defined a priori. The primary outcome assessed was the occurrence of IBD, CD, or UC in patients receiving vaccination compared with patients without any vaccination. The meta-analysis evaluated different types of vaccines against tetanus, poliomyelitis, diphtheria, pertussis, smallpox, measles, mumps, rubella, and tuberculosis (BCG). Most of the studies analyzed the risk of developing IBD independently for each vaccine in the same patient population without reporting a global risk after vaccination. In these studies, each patient may have received 1 or more vaccine types. Because it was not possible to pool the risk of all vaccines for each study, we performed the meta-analysis for each vaccine type separately.

Data Extraction

All data were extracted by the lead investigator to a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA) as an odds ratio (OR) of developing IBD for each vaccine type in each study. If not available, the OR was calculated using the number of cases and controls exposed or not. In addition, the following clinical data were extracted for each study, when available: number of centers, country of origin, geographic region, type of study, inclusion period, inclusion criteria, methods for collecting past vaccination data, matching characteristics for case–control studies,

disease type (UC or CD), total number of controls and IBD cases, and studied vaccines.

Statistical Analysis

Pooled results were expressed as the OR of IBD with vaccination compared with no vaccination, with 95% confidence intervals (CIs). Analyses were performed if at least 3 studies evaluating the same vaccination could be combined. If only 1 or 2 studies investigated the same vaccination, a description of studies was performed without a meta-analysis. Each meta-analysis was performed using only case-control studies, except for the measles vaccination, in which case-control and cohort studies were included in an analysis stratified by study design. For each meta-analysis, the method of Der Simonian and Laird²⁶ was used. According to this method, studies were considered as a random sample from a population of studies. Statistical heterogeneity was tested for each analysis. Because of heterogeneity among studies, a random-effect model was used to analyze data. All analyses were performed using R software and metafor package (R Development Core Team, 2011; R Foundation for Statistical Computing, Vienna, Austria).²⁷

Results

Literature Search

The search strategy identified 428 citations, and 412 articles were excluded after reviewing the title and abstract (Supplementary Figure 1). Sixteen studies were retrieved for evaluation and 5 studies were excluded. Three studies were epidemiologic studies on IBD incidence during a vaccination campaign without estimation of the risk, 1 study was a case report, and 1 study did not have a control group. Finally, 11 studies were included in this systematic review and meta-analysis,^{11–21} and the characteristics of these studies are presented in Table 1. There were 8 case-control studies,^{11,14–18,20,21} of which 6 were population-based^{11,14,15,18,20,21} and 2 were hospital-based,^{16,17} and 3 were population-based cohort studies,^{12,13,19} including 3 cohorts reporting data on measles and on H1N1 influenza. Two studies investigated the occurrence of IBD in the pediatric population only.^{11,20} These studies reported on 11 vaccine types, against tuberculosis (BCG), diphtheria, tetanus, poliomyelitis, smallpox, pertussis, measles, rubella, mumps (including the MMR vaccine), and H1N1 influenza. All of these studies except 1 (H1N1 vaccine) investigated the effect of childhood vaccination. Because most of the studies analyzed the risk of developing IBD independently for each vaccine in the same patient population without reporting a global risk after vaccination, we performed the meta-analysis for each vaccine type separately (Table 2).

Bacille Calmette–Guérin

Three case-control studies (n/4 963 patients) investigated the risk for IBD after BCG vaccination during childhood.^{11,18,21} The relative risk (RR) of developing IBD after BCG vaccination was 1.04 (95% CI, 0.78–1.38). These figures were 1.17 (95% CI, 0.58–2.38; n/4 3 studies; 563 patients) and 0.98 (95% CI, 0.73–1.30; n/4 2 studies; 400 patients) for CD and UC, respectively (Figure 1). There was heterogeneity only among studies on CD (I^2 1/4 62%; P 1/4 .07).

Diphtheria- and Tetanus-Containing Vaccines

Three case-control studies (n/4 524 patients) investigated the risk of developing IBD after diphtheria or tetanus vaccination during childhood with 1 of these studies investigating only pediatric IBD.^{16,18,20} The RRs of developing IBD after vaccination with diphtheria-containing vaccines and tetanus-containing vaccines were 1.24 (95% CI, 0.80–1.94) and 1.27 (95% CI, 0.77–2.08), respectively (Figure 1). No heterogeneity was observed between the 3 studies.

Poliomyelitis

Three case-control studies (n/4 666 patients) investigated the risk of developing IBD after a poliomyelitis vaccination during childhood^{11,18}; 1 study was published only as an abstract.²⁰ The pooled RR of developing IBD after poliomyelitis vaccination was 1.79 (95% CI, 0.88–3.66) (Figure 2A). The specific RRs of developing CD (n/4 345) and UC (n/4 174) were 2.28 (95% CI, 1.12–4.63) and 3.48 (95% CI, 1.24–9.71), respectively (Figure 2B). The exclusion of the study available only as an abstract and without details on risk for CD or UC did not change our results with a pooled RR of 2.61 (95% CI, 1.46–4.68; P 1/4 .0012; and I^2 0% P 1/4 .7817, respectively). There was significant heterogeneity between the studies (I^2 1/4 67%; P 1/4 .049) (Figure 3).

Pertussis

Two case-control studies (n/4 407 patients) investigated the risk of developing IBD after a pertussis vaccination during childhood.^{16,18} The first study, which included 140 IBD patients born after 1968 in the United Kingdom and receiving a pertussis vaccination until 6 years of age, did not find a significant association between vaccination and the risk of developing IBD (OR, 1.00; 95% CI, 0.62–1.62).¹⁶ The second study from Denmark investigated childhood pertussis vaccinations in 267 patients diagnosed with IBD during 2003 to 2004 and matched controls.¹⁸ In this study, vaccination against pertussis increased the risk of developing IBD, especially UC (combined OR, 2.08; 95% CI, 1.07–4.03).¹⁸ Because only 2 studies were available, we did not perform a meta-analysis.

Table 1. Characteristics of Case–Control and Cohort Studies Included in the Meta-Analysis

Study	Year	Country	Type	Population studied	Outcome	Methods for vaccine recall	Matching	Disease	Type of vaccine
Case-control studies									
Gilat et al ¹⁷	1987	International (United States, United Kingdom, Sweden, Holland, Denmark, Israel, France, Italy)	Hospital-based	IBD patients started <20 y, <25 y at the time of the study, at least 6 months duration	Diagnosis of IBD	Self-completion questionnaire	1:2, sex, age	CD	Smallpox, polio, BCG, diphtheria, measles, pertussis, tetanus
Feeney et al ¹⁶	1997	UK monocentric	Hospital-based	Born in or after 1968	Diagnosis of IBD	Data extraction from database	1:2, sex and year of birth	IBD	Pertussis, diphtheria, tetanus, measles
Davis et al ¹⁵	2001	US multicenter	Population-based	1958–1989	IBD and cases from age 6 mo to index date (diagnosis) or reference date for controls	Data extraction from database	1:5, sex, center, year of birth	IBD	Measles, MMR vaccine
Baron et al ¹¹	2005	France multicenter	Population-based	1988–1997	IBD occurring before age 17 y	Personal interview by trained investigators of mother and child (vaccine certificate needed)	1:1, age, sex, living area	IBD	MMR vaccine, BCG, poliomyelitis, smallpox
Bernstein et al ¹⁴	2006	Canada monocentric	Population-based	NA	IBD < 50 y	Questionnaire and venipuncture	None	IBD	Measles, mumps, rubella ^a
Hansen et al ¹⁸	2011	Denmark monocentric	Population-based	2003–2004	Diagnosis of IBD during inclusion period	Questionnaire-based study	Age, sex, ethnicity, geographic location	IBD	Pertussis, diphtheria, tetanus, poliomyelitis, BCG, measles, rubella
Shaw et al ²⁰	2012	Canada multicenter	Population-based	1988–	IBD born after 1989 and diagnosis before 2008	Data extraction, vaccination complete vs incomplete or none by age 2 y	Age, sex, living area at time of diagnosis	IBD	Diphtheria, tetanus, poliomyelitis, MMR vaccine
Villumsen et al ²¹	2013	Denmark (Copenhagen)	Population-based	Children born between 1965 and 1976	Incidental diagnosis of IBD (1977–1994)	Data extraction from database	Age, sex	CD	BCG, smallpox

Cohort studies	1995 UK multicenter	2000 UK multicenter	2011 Sweden monocentric
Thompson et al ¹²	Use of a 1964 cohort of children aged 10–24 mo	Population-based Nationwide	Population-based
Morris et al ¹⁹	People born during the first week of April 1970	People vaccinated during the 2009 campaign	People vaccinated during the 2009 campaign
Bardage et al ¹³	Incidental diagnosis of IBD	Incidental diagnosis of IBD	Diagnosis of IBD during the follow-up period (10 mo)
	Data extraction from database	Postal self-completion survey in 1995–1996	Data extraction from database
	Parallel children cohort for control	None	None
	IBD	IBD	IBD
	Measles	Measles	H1N1 influenza

^aThis study investigated measles, mumps, and rubella serology.

Smallpox

Three case–control studies (n/4 1255 patients) investigated the risk of developing IBD after a smallpox vaccination.^{17,21} The pooled RR of developing IBD after a smallpox vaccination was 1.08 (95% CI, 0.70–1.67; *P* .72), without heterogeneity between the studies (Figure 4).

Measles, Rubella, and Mumps Vaccines

Eight studies (n/4 1366 patients) investigated the risk of developing IBD after measles or MMR vaccination.^{11,12,14–16,18–20} Four studies investigated vaccination against measles with only live or attenuated vaccines,^{12,16,18,19} 2 studies investigated only MMR vaccine,^{11,20} and 1 study investigated both vaccination strategies¹⁵ (Table 2). One other study focused on measles, rubella, and mumps serology, considering that most of the patients were seropositive because of childhood immunization (Table 2).¹⁴ Because 2 studies were population-based cohort studies^{12,19} a meta-analysis of measles-containing vaccines was stratified by study design.

The pooled RRs of developing IBD after measles-containing vaccines in cohort and case–control studies were 1.33 (95% CI, 0.31–5.80) and 0.85 (95% CI, 0.60–1.20), respectively (Figure 4). In the meta-regression, results of cohort and case–control studies were not statistically different. The pooled RR of developing IBD after measles-containing vaccines (MMR included) by pooling cohort and case–control studies was 0.97 (95% CI, 0.63–1.49; *P* ¼ .89) (Figure 4). There was significant heterogeneity between the studies (*I*² ¼ 74%; *P* < .001) (Figure 3); this heterogeneity was owing mostly to cohort studies with an *I*² of 91% (*P* < .001) and 45% (*P* ¼ .1023) for cohort and case–control studies, respectively (Figure 4).

The RRs of developing IBD after a measles vaccination and MMR vaccination in case–control studies were 0.97 (95% CI, 0.73–1.30; *P* .82) and 0.67 (95% CI, 0.36–1.24; *P* ¼ .199), respectively. No heterogeneity was observed between the studies. The RR of developing IBD after vaccination with rubella-containing vaccines (MMR included) was 0.65 (95% CI, 0.33–1.25; *P* .19). There was significant heterogeneity between the studies for rubella-containing vaccines (*I*² ¼ 77%; *P* ¼ .002). Sensitivity analysis excluding the study using serology and not vaccination¹⁴ did not change the results (data not shown).

H1N1 Vaccine

Only 1 study investigated the risk of developing IBD after vaccination against the H1N1 influenza virus (Pandemrix, GlaxoSmithKline, London, UK) during the 2009 vaccination campaign in Sweden.¹³ It was a prospective population-based cohort study comparing the frequency of incident autoimmune diseases in patients

Table 2. ORs of Developing IBD According to Vaccine Type in Case–Control and Cohort Studies

Study	Total cases, n	Vaccine type	Disease	Cases, n		Controls, n		OR	95% CI	
				Vaccinated	Unvaccinated	Vaccinated	Unvaccinated			
Gilat et al ¹⁷	499	Smallpox	CD	266	36	922	76	0.61	0.39–0.95	
Thompson et al ¹²	54	Live measles vaccine	CD	14	15	3531	11392	3.01	1.45–6.23	
			UC	11	14	3534	11393	2.53	1.15–5.58	
Feeney et al ¹⁶	140	Pertussis	IBD	99	41	198	82	1.00	0.62–1.62	
			Diphtheria/tetanus	IBD	130	10	261	19	0.94	0.39–2.26
			Measles	IBD	79	61	160	120	0.97	0.64–1.47
Morris et al ¹⁹	52	Measles	IBD	35	17	7284	2421	0.62	0.3–1.2	
			CD	20	10	7299	2428	0.67	0.3–1.6	
			UC	15	7	7304	2431	0.57	0.2–1.6	
Davis et al ¹⁵	142	MMR	IBD	94	10	300	23	0.59	0.21–1.69	
			Measles-containing vaccines	IBD	38	10	109	23	0.97	0.21–1.69
Baron et al ¹¹	282	MMR vaccine	CD	-	-	-	-	0.5	0.35–0.90	
			CD	-	-	-	-	2.8	1.1–7.2	
			Poliomyelitis	CD	-	-	-	-	2.6	1.1–6.2
			UC	-	-	-	-	7	1.1–151	
			Smallpox	CD	-	-	-	-	2.1	1.00–4.30
			UC	-	-	-	-	10	1.3–208	
Bernstein et al ^{14,a}	372	Measles	CD	226	9	304	6	0.90	0.30–2.80	
			UC	131	6	304	6	0.40	0.10–1.40	
		Mumps	CD	170	65	243	67	0.90	0.60–1.40	
			UC	130	7	243	67	0.90	0.60–1.50	
		Rubella	CD	214	21	304	6	0.20	0.10–1.40	
			UC	128	9	304	6	0.30	0.10–1.00	
Hansen et al ¹⁸	267	Diphtheria	IBD	-	-	-	-	1.33	0.63–2.82	
			IBD	-	-	-	-	2.08	1.07–4.03	
			IBD	-	-	-	-	1.30	0.76–2.25	
			IBD	-	-	-	-	2.38	1.04–5.43	
			IBD	-	-	-	-	1.29	0.73–2.27	
			IBD	-	-	-	-	1.60	0.52–4.89	
			IBD	-	-	-	-	0.95	0.50–1.81	
Bardage et al ¹³	14,842	H1N1 influenza	IBD	8784	6058	1,015,235	914,947	1.13	0.97–1.32	
Shaw et al ²⁰	117	Diphtheria/tetanus	IBD	102	15	692	142	1.40	0.70–2.90	
			IBD	48	69	334	500	1.00	0.60–1.70	
			IBD	113	4	784	50	1.50	0.50–4.30	
Villumsen et al ^{21,b}	474	BCG	CD	160	58	132,321	46,271	0.95	0.67–1.35	
			UC	186	70	132,638	46,236	0.95	0.70–1.29	
		Smallpox	CD	125	93	100,435	78,156	1.13	0.77–1.67	
			UC	130	126	100,819	78,055	0.92	0.64–1.32	

^aResults are shown for measles, mumps, and rubella serology.

^bControls are expressed in person-years.

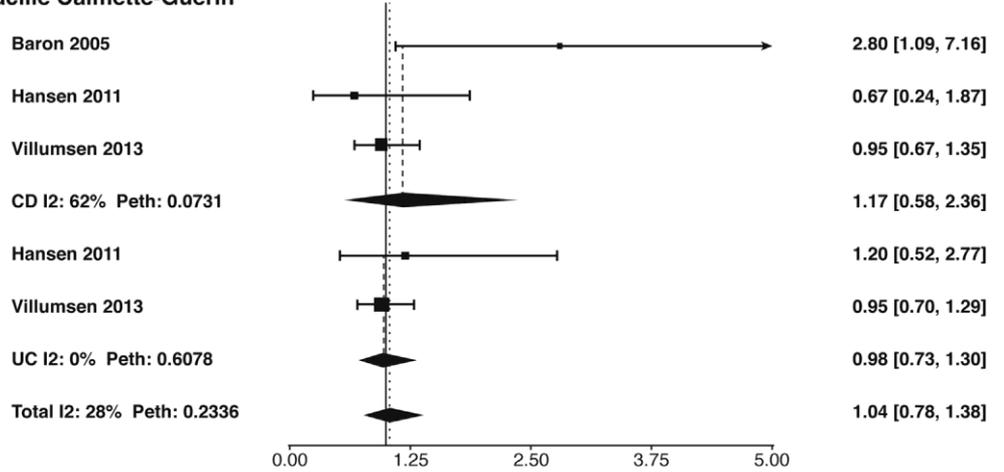
with or without vaccination.¹³ After adjusting the statistical model for age, sex, socioeconomic status, and health care consumption (number of hospital admissions and visits to specialist care 1 year before the pandemic period), the hazard ratio of developing IBD after the H1N1 vaccination was 1.13 (95% CI, 0.97–1.32).¹³

Discussion

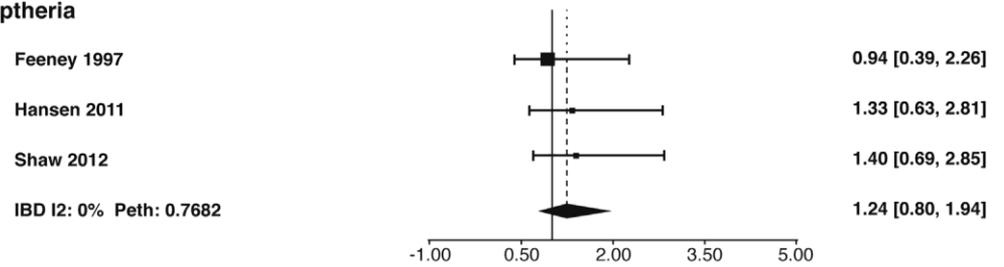
Since the report by Thompson et al,¹² the controversy about the risk of developing IBD after childhood immunization still is ongoing. This study reported that vaccination with the live measles vaccine was a risk for the development of consequent inflammatory disease, such

as CD or UC. However, many publications after this report investigating vaccination with measles-containing vaccines did not show any association between immunization and IBD. Epidemiologic studies also investigated other vaccines such as BCG, diphtheria, tetanus, poliomyelitis, smallpox, pertussis, rubella, and mumps, reporting conflicting results. A positive association between BCG vaccination and CD were found in the study by Baron et al,¹¹ with a high risk in patients with multiple immunization shots. This study also found a positive association between poliomyelitis and smallpox vaccination and CD.¹¹ One 2011 population-based, case–control study found a positive association between pertussis and poliomyelitis vaccination and risk for IBD.¹⁸ On the contrary, 1 hospital-based, case–control

Bacille Calmette-Guérin



Diphtheria



Tetanus

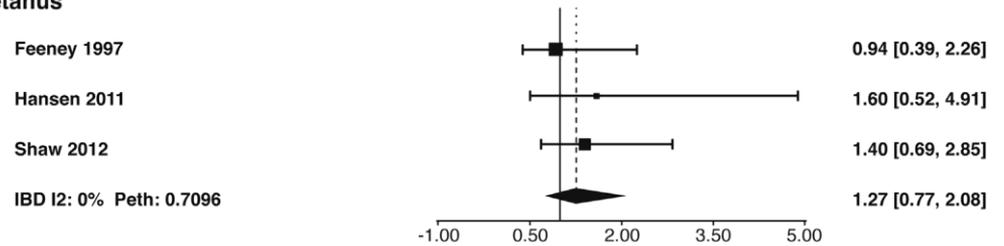
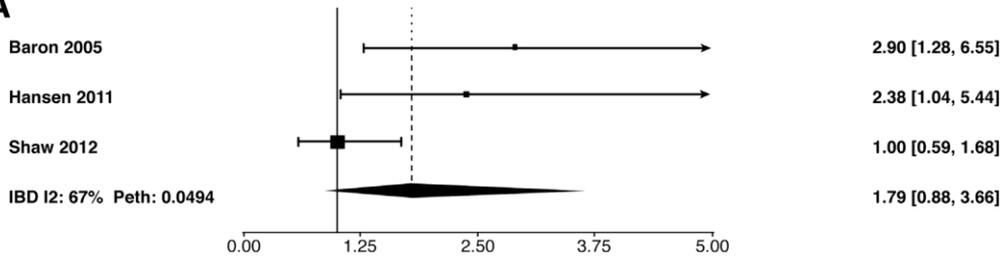


Figure 1. Risk ratio of developing IBD after BCG, diphtheria, and tetanus vaccinations in case-control studies.

Poliomyelitis

A



B

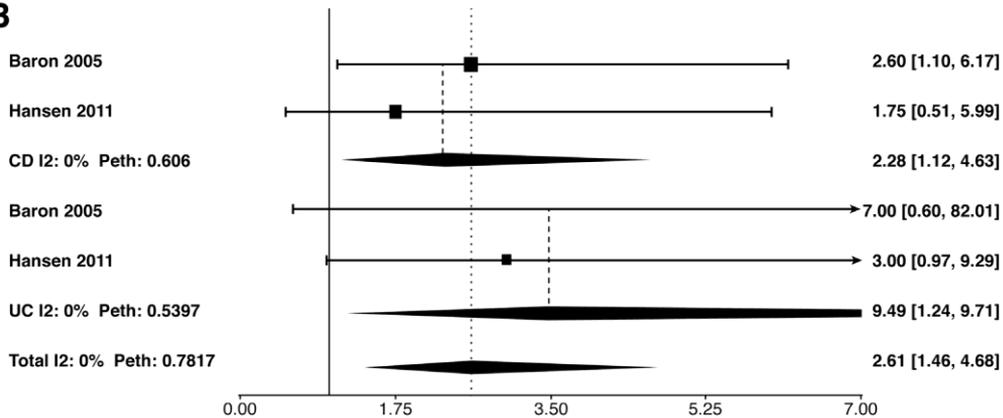


Figure 2. Risk ratio of developing IBD after poliomyelitis vaccination in case-control studies. (A) Meta-analysis using all studies reporting the risk for IBD. (B) Meta-analysis with studies reporting the specific risk for Crohn's disease and ulcerative colitis.

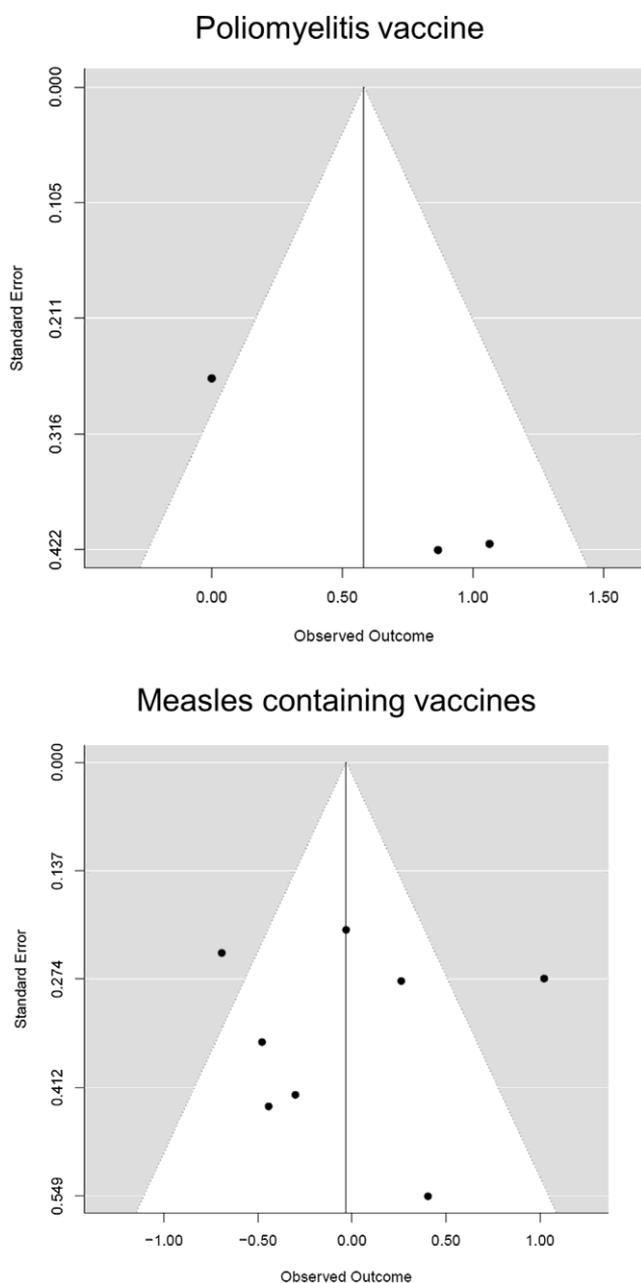


Figure 3. Funnel plots for poliomyelitis and measles vaccines.

study published in 1987 found a protective role of smallpox vaccination against CD.¹⁷

Including 11 studies, 8 case–control studies, of which 6 were population-based and 2 were hospital-based, and 3 population-based cohort studies, we performed a meta-analysis of the risk of developing IBD after childhood or adult vaccination. Of note, the majority of the studies included focused only on childhood vaccination and 1 study investigated the H1N1 vaccine in adults. Overall, our results did not find any significant increased risk of developing IBD after childhood immunization with BCG, diphtheria, tetanus, poliomyelitis, smallpox, pertussis, measles, mumps, and rubella-containing vaccines. The study that investigated H1N1 vaccination in adults did not find any significantly increased risk of developing

IBD after this vaccination. Regarding poliomyelitis vaccination, 2 of the 3 studies analyzed in the meta-analysis reported a significant risk of developing IBD after vaccination. The other study was published only as an abstract and did not provide details for CD and UC. When we performed a sensitivity analysis without the study published as an abstract, we found a positive association between poliomyelitis vaccination and the risk of developing CD or UC (2.28 [95% CI, 1.12–4.63] and 3.48 [95% CI, 1.24–9.71], respectively). Regarding pertussis vaccination, only 2 studies reported a risk of developing IBD, with conflicting results.^{16,18}

The results of this meta-analysis are globally reassuring regarding the risk of developing IBD after childhood vaccination. Vaccines that are developed to protect against an infectious disease or its consequences are, for the majority, not a risk for the subsequent development of intestinal inflammatory disease. The strength of our study was the large number of patients included in the meta-analysis, with 2399 IBD patients and 33,747 controls in 10 studies investigating 10 vaccine types (BCG, diphtheria, tetanus, poliomyelitis, smallpox, pertussis, measles, rubella, mumps, and the MMR vaccine), although not all vaccines were investigated in each IBD patient. The study investigating the H1N1 vaccine included 14,842 patients with IBD. Limitations of our work mainly were owing to the fact that studies investigating the risk of developing IBD after vaccination were extremely heterogeneous regarding their study design, sample size, geographic location, and vaccination recall methods. Indeed, we found significant heterogeneity between the studies for poliomyelitis- and measles-containing vaccines. Vaccination protocols varied between countries and evolved through the years, with different types of vaccines and schedules leading to difficulties in risk evaluation. Moreover, some vaccines used were live attenuated vaccines such as measles, oral poliomyelitis, or whole-cell pertussis vaccines, and may have a different effect on immune system activation and dysregulation compared with other inactivated acellular vaccines. In addition, the method of recalling the vaccination status in each patient represented a limitation in these studies. Indeed, half of the studies used a database to collect the vaccination status of patient, but the other half used only a self-completed questionnaire or an interview, which may have led to recall bias. Specific bias present only in certain studies could have led to heterogeneity as well as publication bias because statistically significant results come mostly from smaller studies,^{11,12,18} as illustrated by the Funnel plot profile for poliomyelitis. However, the small number of studies for most vaccines did not allow us to explore further publication bias and heterogeneity. Of note, the study by Gilat et al,¹⁷ which collected data about several vaccinations, only reported detailed positive results for smallpox vaccination, indicating that no association was found for the other vaccines without providing any detail. A major limitation of the study was that all the

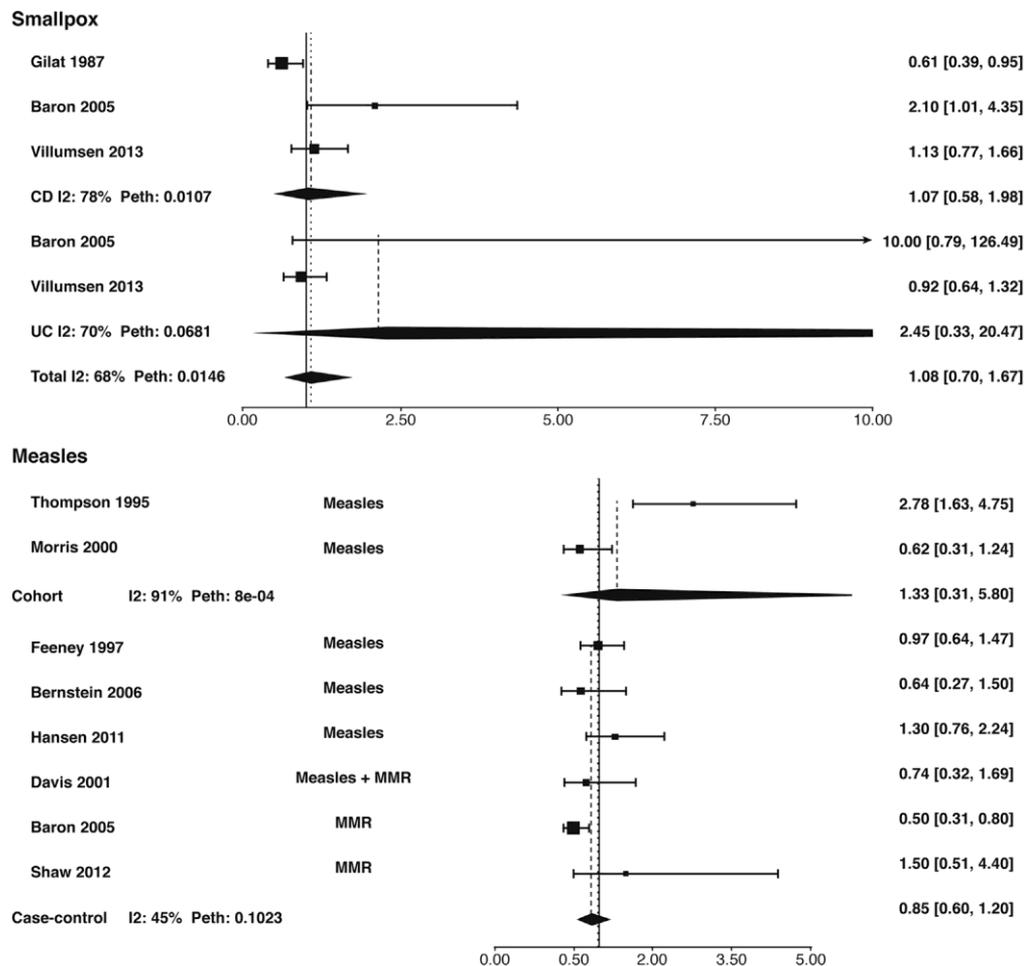


Figure 4. Risk ratio of developing IBD after smallpox and measles vaccinations in case-control and cohort studies.

case-control studies included in the meta-analysis evaluated more than 1 vaccine at a time and that it was not possible to determine specifically the risk related to only 1 vaccine. Individuals with multiple vaccinations may be at higher risk for IBD, as suggested in the study by Baron et al.¹¹

In this meta-analysis, although the overall analysis of all studies investigating the poliomyelitis vaccination did not find any increased risk of developing IBD, sensitivity analysis indicated that patients receiving the poliomyelitis vaccine may be at risk for developing CD or UC. Indeed, 2 studies showed an increased risk of developing IBD after childhood vaccination with the poliomyelitis vaccine^{11,18} and only 1 study published as an abstract did not find a significantly increased risk.²⁰ The poliomyelitis vaccine is used widely in developed countries and mostly combined with diphtheria- or tetanus-containing vaccines.^{28,29} These 3 national studies investigating the poliomyelitis vaccination did not provide any detail on the route of administration of the vaccine, which may be a critical factor to explain differences in results.^{11,18,20} Indeed, 2 types of poliomyelitis vaccine, an oral live vaccine (OPV) and an injected inactivated vaccine (IPV) have been used during the past decades worldwide to eradicate poliomyelitis.²⁸ We may hypothesize that live attenuated OPV may have a greater

impact on activating the mucosal immune system than the IPV, and have different effects on the risk of IBD. Although publications did not contain any information about the route of administration, extrapolation could be made by looking at public vaccination history in involved countries.^{28,30,31} In the French study by Baron et al¹¹ patients were recruited beginning in 1988 and should have received the IPV because France had withdrawn the utilization of the OPV since 1983. In Denmark, combined vaccination with OPV and IPV has been practiced since 1966 and has been replaced only recently with IPV vaccination alone.³⁰ Patients in the Danish study by Hansen et al¹⁸ all would have been vaccinated with the IPV. In Manitoba, Canada, after having adopted a mixed schedule of IPV and OPV since 1962, switched to an exclusive OPV schedule during the 1970s. Then, between 1994 and 1997 Manitoba transitioned to the exclusive use of the IPV.²⁸ Therefore, we may hypothesize that the majority of patients in the Canadian study from Shaw et al²⁰ (pediatric IBD cases in Manitoba born after 1989 and diagnosed before 2008) may have received only the OPV. This difference in vaccine type if true may explain the contradictory results of these studies. Heterogeneity in the meta-analysis results also could be explained by differences in study design (2 studies investigated only pediatric IBD patients^{11,20}) or in the samples (the study

by Shaw et al²⁰ had half as many IBD cases as the 2 other studies^{11,18}). Moreover, methods for vaccination recall were different between these studies, with positive studies using questionnaires and the negative study using a population-based database of immunizations administered in Manitoba. In addition, the IPV contains many adjuvants that may be involved in stimulation of the immune system.²⁴ Indeed, vaccine adjuvants such as thimerosal and aluminum, the 2 major salt-based adjuvants that have been used or still are used in vaccines, may participate in the development of inflammatory disorders.^{10,32} Thimerosal, an ethyl mercury-containing compound that has been used as a preservative in multidosed vials of vaccines to prevent bacterial and fungal contamination of those vials, now has been removed completely from vaccines whereas aluminum salts used to boost the immune response still are present in most of the vaccines used in children. Both thimerosal and aluminum have been suspected to be involved in various inflammatory or neurologic disorders.^{10,32} Thus, the lack of data about the exact composition of vaccines used in these studies has led to difficulty in interpreting results.

We also found conflicting results on pertussis vaccination and the risk of developing IBD in 2 studies.^{16,18} There was no information about the type of pertussis vaccine, but during the study period in the United Kingdom and Denmark a whole-cell pertussis vaccine was used exclusively.^{33,34} Other differences in the design of these studies may explain the conflicting results because the UK study was hospital-based whereas the Danish study was population-based. Moreover, in the study by Hansen et al,¹⁸ poliomyelitis virus found to be associated with an increased risk of IBD may act as a confounding factor. Interestingly, the UK study by Feeney et al¹⁶ did not report on poliomyelitis vaccination and during the study period only the OPV was used in the United Kingdom.

In conclusion, results of this meta-analysis do not support a role of childhood immunization or H1N1 vaccination in the development of IBD. The association between the poliomyelitis vaccine and risk for CD or UC should be analyzed cautiously because of study heterogeneity and will require further investigation.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <http://dx.doi.org/10.1016/j.cgh.2015.04.179>.

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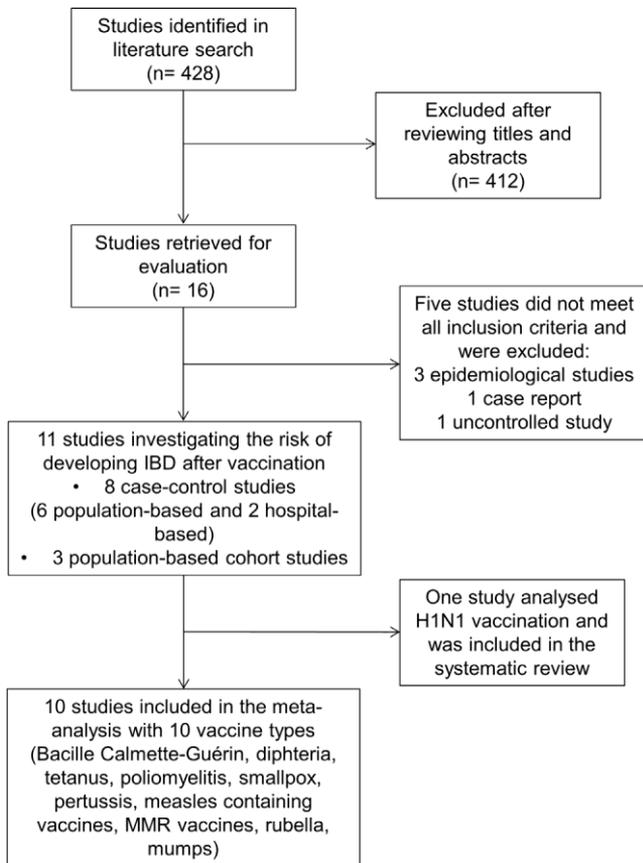
Address requests for reprints to: Guillaume Pineton de Chambrun, MD, PhD, Gastroenterology and Hepatology Department, Montpellier University Hospital, 80 Avenue Augustin Fliche, F-34000, Montpellier, France. e-mail: gpinetondechambrun@yahoo.fr; fax: (33) 4-67-33-75-75.

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Conflicts of interest

The authors disclose no conflicts.



Supplementary Figure 1. Flow chart.