MMR vaccination and autism: no indication for an association

Horizon scanning report

Gezondheidsraad
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

Subject : presentation of Horizon scanning report *MMR vaccination and autism: no indication for an association*
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Dear Minister,

Enclosed please find the report *MMR vaccination and autism: no indication for an association*, presented by the Committee of the Health Council of the Netherlands on Side Effects of Vaccinations. The Committee was assisted in its deliberations by Prof. J.K. Buitelaar, professor of Psychiatry at the St Radboud University Medical Centre in Nijmegen. The document was reviewed by the Standing Committees on Medicine and Infection & Immunity of the Health Council.

The reason for reviewing a possible link between MMR vaccination and autism was the concern raised a number of years ago by a publication in the medical journal The Lancet, in which the English gastroenterologist Andrew Wakefield and other authors suggested the existence of a link between MMR vaccination and autism.

In preparation of this report, the scientific studies performed in response to this publication have been reviewed by the Committee. The Committee's main conclusion is that it has not found any evidence that MMR vaccination causes, promotes or exacerbates autism. I agree with this conclusion of the Committee.

In this report, the Committee only discusses autism to the extent required for its study of the relevant scientific literature. The topic of autism in a wider sense is covered in a separate report.

Yours sincerely,
(signed)
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to:

the Minister of Health, Welfare and Sport

No. 2007/04E, The Hague, January 25, 2011

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Contents

Executive summary

In the Netherlands, all children above the age of 14 months are vaccinated against mumps, measles and rubella (or German measles). This is the so-called MMR vaccination. This approach prevents numerous cases of these diseases in children every year. There is widespread acceptance of this inoculation.

Nevertheless, over the past few years, there has been some disquiet about possible adverse effects. It all started in 1998, with the publication of an article by the British gastroenterologist Andrew Wakefield and co-workers, in the medical journal *The Lancet*. In this article, they described the cases of twelve children with behavioural problems, eight of whom were ultimately diagnosed as suffering from 'autism'. Some of these children's parents or GPs link the onset of their behavioural problems to the MMR vaccination. Following the publication of the article in *The Lancet*, there was a sharp increase in scientific research into a link between the MMR vaccination and the development of autism.

What is the current level of scientific knowledge regarding a possible link between the MMR vaccination and autism? How likely is it that any such link exists, given the available scientific knowledge? These questions are addressed here.

In this horizon scanning report, the Health Council of the Netherlands' Committee on adverse reactions following vaccinations under the National Immunisation Programme lists the results of these follow-up studies. It does so by testing the

publications in question (which involved in some cases very large groups of children from Denmark, Finland, Japan, the United Kingdom, and the United States).

The Committee's findings are that autism does not occur more frequently among individuals who have had an MMR vaccination, and that the increase in the MMR vaccination level cannot be linked to an increase in autism. It also found that there is no temporal link between the development of autism and administration of the MMR vaccination, nor is the MMR vaccination associated with a novel form of autism. The Committee has found no evidence that the MMR vaccination either causes, promotes or aggravates autism. In the Committee's view, the hypotheses concerning the biological mechanism underpinning the alleged link between MMR vaccination and autism are purely theoretical in nature.

Finally, the Committee would like to emphasise the importance of the MMR vaccination. A decline in the vaccination level in the Netherlands, as a result of the disquiet about alleged adverse effects for example, could lead to an increase in mumps, measles, or rubella. The associated disease and mortality could be prevented by administering the vaccination.

Chapter 1

Introduction

1.1 Background to this report

Once they are over 14 months old, all children in the Netherlands are vaccinated against measles, mumps and rubella (or German measles), using a combined MMR vaccine that has been part of the Dutch National Immunisation Programme since 1987.[1] This vaccination prevents numerous cases of these diseases in children every year, and is widely accepted by the Dutch population.

Nevertheless, in recent years, there has been some concern about the onset of autism as a possible side effect. This started with the publication of an article in the English medical journal *The Lancet* in 1998, in which the British gastroenterologist Andrew Wakefield described the cases of twelve children with behavioural problems, some of whom were ultimately diagnosed as autistic.[2] Some of these children's parents of GPs linked the onset of the behavioural problems to the MMR vaccination. The publication in The Lancet led to a marked increase in the scientific investigation of a possible link between MMR vaccination and autism.

These developments led the Committee on Side Effects of Vaccinations, one of the permanent Committees of the Health Council of the Netherlands, to study this topic.

Until recently, the main task of the Committee was to review the data collected by the Dutch National Institute for Public Health and the Environment (Dutch abbreviation RIVM) and to assess reports of suspected side effects of vaccinations carried out within the framework of the Dutch National Immunisation Programme. The Committee has produced a number of reports on this topic of recent years.[3,4]

Another, more recent task is to closely monitor the latest scientific knowledge on suspected side effects of vaccinations. The present report is the first fruit of this branch of the Committee's activities. In Annex A the members of the Committee are named.

1.2 Structure of this report

The report consists of three chapters, each dealing with a specific question:

1 What clinical pictures are covered by the term 'autism'?
2 What is the current state of scientific knowledge about a possible link between MMR vaccination and autism?
3 What is the Committee's assessment of the likelihood of the existence of a link between MMR vaccination and autism?

Chapter 2

Autism Spectrum Disorders (ASD)

2.1 Characteristics

Children with autism spectrum disorders (also known as pervasive developmental disorders) are characterised by qualitative impairments of social interaction and communication and by stereotypical patterns of behaviour, interest and activity.[5] The following types of ASD, among others, may be distinguished on the basis of these characteristics and other criteria: classical autism, Asperger syndrome and pervasive developmental disorder not otherwise specified (PDD-NOS), which is also known as atypical autism.

The diagnosis of a specific autism spectrum disorder in children may be made on the basis of the criteria laid down by the World Health Organisation (WHO) or the American Psychiatric Association (APA).[6,7]

2.2 Definitions

The scientific literature on studies of a possible link between vaccination and autism uses different definitions of the clinical pictures involved, which do not always agree with those of the WHO or the APA. Nearly all authors use the diagnosis ‘autistic disorder’ and the term ‘autistic spectrum disorder’ as a collective name for all autistic conditions.

In its description of the various studies of a possible link between MMR vaccination and autism, the Committee adopts the terms used by the authors in question. When weighing the results it uses the widely recognised term ‘autism’ as a collective name for all the conditions involved, in preference to the term ‘autistic spectrum disorders’ or ‘pervasive developmental disorders’.

2.3 Prevalence

The prevalence of autism is difficult to determine. Older studies yield a lower prevalence than more recent ones. It is not clear, however, whether this increase in the number of children reported with autism reflects a real increase in the prevalence.[5,8,9] Firstly, the definitions of autism and the conditions falling under this common denominator have changed in the course of time and have expanded – especially in the case of the milder conditions – thus leading to growth of the overall patient group.[8,9] There are also indications that improved diagnostic methods have led to an increase in the number of patients reported.[9] Furthermore, the prevalence of the individual clinical pictures reported in the more recent publications varies widely.[10-13]

Several authors state that an incidence of from three to six children per thousand is the most likely.[14,15]

2.4 Cause

Autism is the collective name of a range of clinical pictures whose definition is based on abnormal behavioural patterns. No clearly defined cause can be identified. Genetic factors probably play the main role in the development of autism, but environmental influences cannot be excluded.[5,16]

Chapter 3

Investigation of the link between vaccination and autism

3.1 First publication

In 1998, Andrew Wakefield *et al*. published a description of twelve children with behavioural problems and chronic colitis in the English medical journal *The Lancet*.[2] The parents or the GP of six of the eight children ultimately diagnosed with autism perceived a link between the onset of the behavioural problems and the MMR vaccination. The same link was stated to be present in the case of the child with autism as the likely diagnosis, and of the child with the postulated diagnosis of post-vaccinal encephalopathy.

The behavioural problems were reported to have started from one to fourteen days after the MMR vaccination, with an average delay of 6.3 days, and were preceded by colitis. The authors suggested that the mechanism responsible for their findings might be the development of colitis due to the vaccination, leading to enhanced intestinal permeability for proteins. These proteins could then have an effect on the brain, leading to behavioural changes. Previous publications by Wakefield reported the presence of fragments of the measles virus in patients with chronic colitis.[17,18]

In a commentary accompanying the article by Wakefield *et al.*, Chen and DeStefano from the Centers for Disease Control in the United States stated that initial reports of side effects of vaccinations should always be taken very

seriously, since vaccination programmes usually cover very large numbers of healthy young children.[19]

However, the study by Wakefield *et al*. also met with criticism. A general comment was that the measles vaccine has been administered to hundreds of millions of people since the 1960s without the development of behavioural problems and/or colitis. Another general criticism was that the results of studies of this type can be influenced by the fact that the age at which the vaccinations are given is also the age at which autism usually manifests itself.

There was also specific criticism of details of the study by Wakefield *et al*.[19] Chen and DeStefano stated that their patient group was not homogeneous as regards the nature of the colitis and the behavioural problems, and believed that this group was recruited in a selective manner. They also stated that one cannot exclude the possibility that in the case of a complaint like autism, where the moment when the condition first manifests itself is difficult to pinpoint exactly, the parents and the GP may tend to link the first signs of the condition to an unusual event, such as vaccination. Chen and DeStefano claim that at least in some of the reported cases, the behavioural problems actually preceded the colitis, thus supporting this possible explanation for a perceived link.

Finally, Chen and DeStefano queried the mechanism responsible for the effect proposed by Wakefield *et al.*, since various other investigations of the presence of fragments of the measles virus in patients with chronic colitis, where more sensitive detection methods were used than those employed by Wakefield *et al.*, found no evidence that the virus played a role.[20-22] These findings have very recently been confirmed in studies of the persistence of the measles virus in the white blood cells of children with autism.[23,24] An epidemiological investigation of a possible link between measles, or vaccination against this disease, and the development of chronic colitis also failed to reveal any connection.[25,26]

3.2 Further investigation

The article of Wakefield *et al*. has unleashed a whole series of studies of the possible link between vaccination (in particular MMR vaccination) and the development of autism. The Committee reviews the results of these further studies below. The studies are arranged on the basis of the four hypotheses initially used for this purpose by Wilson *et al*.[27] These hypotheses are:

1 Autism occurs more often in individuals who have been given the MMR vaccine
2 The increase in the level of MMR vaccination leads to an increase in autism

3 There is a temporal relationship between the development of autism and administration of the MMR vaccine
4 MMR vaccination is associated with a new form of autism.

Hypothesis 1: autism occurs more often in individuals who have been given the MMR vaccine

This is the most obvious of the four hypotheses considered. It is however difficult to test, since large study groups are required for this purpose, and vaccination coverage is so high in most Western countries that it is difficult to find enough unvaccinated children to use as controls.

The Committee is only aware of one study of sufficient size in this category. Madsen and co-workers investigated all children born in Denmark between 1991 and 1998.[28] Of the 537 303 children in question, 82 per cent (440 655 children) had been given MMR vaccination. Three hundred and sixteen children were diagnosed with 'autistic disorder', and 422 with 'other autistic spectrum disorders'. The relative risk of autistic disorder among the vaccinated children as compared with the unvaccinated children was close to unity, the value found being 0.92 (with a 95% confidence interval of 0.68-1.24). The relative risk of other autistic spectrum disorders was 0.83 (95% confidence interval 0.65-1.07). The authors concluded that the results argued against a link between vaccination and autism.

Passive registration systems in which reports of the suspected and corroborated side effects of vaccinations are collected and assessed could also be used as a source of data for testing the hypothesis that autism occurs more often in individuals who have been given the MMR vaccine. However, such systems are considered to be less useful for this purpose than studies like that of Madsen *et al.*, because of the lack of control groups.[28] Nevertheless, data from registration systems can give an indication of the existence of side effects.

One such system, to be found in the United States, is the Vaccine Adverse Events Reporting System (VAERS).[29] A Committee of the American Institute of Medicine has studied a number of reports from VAERS concerning the occurrence of autism after vaccination.[30] The Committee concluded that these reports cannot be used as a basis for statements about a possible causal link between MMR vaccination and autism, since systems like VAERS have a number of limitations such as underreporting and a lack of detail in the reports.[29,31]

In the United Kingdom, a working group of the Medicines Control Agency reviewed 111 reports of autism as a suspected side effect of MMR vaccination.[32] It concluded that the available evidence does not support the idea of a causal link between MMR vaccination and autism, but commented that the limitations of the case reports made a more definitive assessment impossible.

In Finland, all reports of suspected and corroborated side effects of MMR vaccination have been collected during the first 14 years after the introduction of this type of vaccination (with a total of 1.8 million vaccinated children), and blood samples have been taken for further analysis from the children with complaints.[33] In total, 173 reports of suspected or corroborated serious side effects have been collected. None of these concerned children with autism.

In the Netherlands, reports of suspected and corroborated side effects of vaccinations performed in the framework of the national vaccination programme, are recorded and assessed by the RIVM, which produces an annual report on these data. The RIVM reports for the years from 1996 up to and including 2004 mention a total of fifteen cases of children with an autistic spectrum disorder.[34-41] In the opinion of the RIVM, none of these disorders was caused or exacerbated by the MMR or other vaccination; in a number of cases, the first signs of the disorders were observed in the children before the vaccination had been given. The Committee reviewed a number of these reports in the framework of its task of reassessing the reports of side effects, and came to the same conclusion as the RIVM.[4]

Hypothesis 2: the increase in the level of MMR vaccination leads to an increase in autism

Most of the studies aimed at testing the second hypothesis made use of time series, in which the percentage of vaccinated children was presented alongside the corresponding incidence of autism as a function of time. In some of the studies described, it was actually possible to link the data on vaccination and autism at an individual level.

Dales and co-workers studied groups of young schoolchildren in the United States.[42] They determined the percentage of children who received MMR vaccination and the percentage treated for an autistic disorder, both as functions of the year of birth. The percentage of vaccinated children was 72 per cent in the 1980 birth cohort and 82 per cent in the 1994 birth cohort, a relative increase of 14 per

cent. The corresponding number of children with an autistic disorder rose from 44 per 100 000 live births to 208 per 100 000 live births, a relative increase of 373 per cent. Although it was not possible to link the individual data on vaccination and autism in this case, the authors nevertheless concluded that the very large difference between the relative increases in MMR vaccination on the one hand and autism on the other did not support a link between these variables.

Kaye and co-workers published the results of a similar study that was carried out in the United Kingdom.[43] They used data from the UK General Practice Research Database and compared the percentage of children receiving MMR vaccination with the incidence of newly diagnosed autistic disorders. This incidence rose between 1988 and 1999 for the study group as a whole from 0.3 per 10 000 person years to 2.1 per 10 000 person years. The incidence in boys aged between two and five years (the group in which previous research found the increase in autistic disorders to be the greatest) rose from 8 per 10 000 for the 1988 birth cohort to 29 per 10 000 for the 1993 birth cohort. The percentage of children receiving the MMR vaccination remained above 95 per cent throughout the entire study period. If the MMR vaccination had been responsible for the increase in autistic disorders, this increase would have levelled off in the years following the introduction of MMR vaccination. Since this effect was not observed, the authors concluded that no correlation exists between MMR vaccination and autism.

Smeeth and co-workers also used data from the UK General Practice Research Database.[44] In their matched case-control study they matched 1294 patients in whom autism had been diagnosed with 4469 controls by age, sex and GP practice. They found the odds ratio (a measure of the relative risk) for a link between MMR vaccination and autism to be 0.86 (95% confidence interval 0.68-1.09), and concluded on this basis that MMR vaccination is not associated with an increased risk of autism.

Taylor and co-workers studied the possible effects of MMR vaccination on 498 children with autism who were born in eight health districts of northeast London in the period from 1979 to 1992.[45] They were able to link the individual data on diagnosis and vaccination, subsequently performing a number of different analyses, the first of which is discussed here (another one will be reported in connection with hypothesis 3). Their analysis revealed that the incidence of autistic disorder and atypical autism increased steadily in the period from 1979 to 1992,

and that the introduction of MMR vaccination in 1988 did not lead to a sudden rise in the rate of increase.

Chen and co-workers carried out a widely based study of the possible link between autism and exposure to measles or various forms of vaccination against measles.46 They also found that the introduction of monovalent measles vaccine was not associated with a stepwise increase in the incidence of autism, and that the introduction of the MMR vaccine or a change in the measles component of this vaccine did not lead to a change either.

The most recent study of a possible link between MMR vaccination and autism in groups of children is that of Honda and co-workers.[47] The special feature of this study is that it was carried out in a population of children that showed a sharp drop in the vaccination level: these children no longer received MMR vaccination, because of the supposed side effects of this intervention. After MMR vaccination was stopped in the Japanese city of Yokohama, the vaccination level dropped from about seventy per cent in the 1988 birth cohort to less than two per cent in the 1992 cohort. The incidence of autistic spectrum disorders rose from 47.6 per 10 000 to 85.9 per 10 000 in the same period, and continued to rise in the period from 1993 to 1996.

Hypothesis 3: there is a temporal relationship between the development of autism and the administration of MMR vaccine

The studies described above that were performed to test hypothesis 2 showed that no association could be found between the increase in autism and the introduction of MMR vaccination in the groups investigated. This cannot however be seen as a definite proof that there is no link between the two. There could be a link between MMR vaccination and autism even in the absence of a rise in the incidence, if MMR vaccination was found to speed up the development of autism in individuals who are predisposed to develop this condition. Two questions can be asked in this connection. Firstly, ‘Is the age at which autism is diagnosed or at which parents first express concern about possible autism different in vaccinated children with autism than in unvaccinated children with autism?’. And secondly, ‘Does MMR vaccination lead to clustering of the moments at which autism is diagnosed, or of events that could be associated with this diagnosis?’.

Investigation of the age at which autism is diagnosed or concerns are first expressed

Fombonne and Chakrabarti compared the age of various groups of children with autism at which parents first expressed concern about signs that could be seen as an indication of this condition.[48] They did not find any difference between the age in two groups of vaccinated children and that in a group of children who had grown up before routine MMR vaccination had been introduced.

Investigation of clustering after vaccination

In a study of neurological disorders after MMR vaccination, Makela and co-workers investigated the association between data on hospital admissions and data on vaccination in a large group of Finnish children (535 441 children, vaccinated in the period 1982-1986).[49] Three hundred and fifty-two of these children were diagnosed with autism. No clustering of hospital admissions for autism after MMR vaccination was found in this study group.

Studies of both questions

The authors of the above-mentioned study of all children born in Denmark between 1991 and 1998, also investigated the age at which concerns were first expressed or a diagnosis was given and possible clustering.[28] The age distribution of vaccinated children at the time they were diagnosed with autism did not differ from that of the unvaccinated children.[28] Furthermore, the moment of diagnosis showed no clustering in time in the vaccinated children as compared with the unvaccinated children.

The study of Taylor and co-workers in eight health districts in northeast London mentioned above in connection with the trials of hypothesis 2 also considers the two questions that are relevant for considering hypothesis 3.45 In order to investigate the moment at which concern was first expressed, the children with an autistic disorder or atypical autism were divided into three groups: children who were vaccinated before the age of 18 months (a total of 233 children), children vaccinated after the age of 18 months (a total of 59) and unvaccinated children (a total of 64). The results showed that early or late administration of the MMR vaccine did not influence the age at which autistic disorder or atypical autism was diagnosed.[45]

In order to detect possible clustering, the researchers used a case series approach to analyse the time when the autism manifested itself, this time being measured in different ways: as the moment of diagnosis, as the moment when the parents first expressed concern about their child's condition, or as the onset of behavioural regression in various periods after MMR vaccination. According to Wakefield *et al*. (who were the first to suggest a link between MMR vaccination and autism), this regression forms part of a special form of autism which they claim to be associated with the MMR vaccination (see hypothesis 4).

Of the twelve periods investigated in the study by Taylor and co-workers, however, the period up to six months after vaccination is the only one where clustering is found – namely clustering of the first expression of concern by the parents. According to the authors, this clustering is due to the combination of a peak in MMR vaccinations around the age of 13 months and a peak – not in itself related to the vaccination – in the first expression of concern about autism by the parents round about the time when the child is 18 months old. The authors concluded that their analyses did not support the existence of a link between MMR vaccination and autism.

The study by Taylor and co-workers was criticised from various perspectives. It was argued, for example, that the use of the case series approach was not appropriate in this investigation, as this approach is more suitable for the study of acute effects than for the study of conditions that develop more slowly, such as autism.[50-52] The authors refuted this criticism in their response.[53,54] They showed in a subsequent publication that even if the data are analysed in another way, the results still do not support the existence of a link between MMR vaccination and autism.[55]

A second point of criticism was the suggestion that the clustering of the first expression of concern by the parents in the period up to six months after the vaccination could have been an artifact.[51] The discussion triggered by this suggestion led to further investigation and to a publication by DeWilde and co-workers.[56] This was based on the hypothesis that if MMR vaccination led in the short term to behavioural problems and eventually to autism – as claimed by Wakefield and co-workers[2] – this should be reflected in an increasing number of visits to the GP in the period after vaccination.

This hypothesis was tested with the aid of data taken from the Doctor’s Independent Network, a database containing data from GP practices that use a certain

software package. The frequency of visits to the GP by 71 patients ultimately diagnosed with autism was compared with that of 284 controls, matched by age, sex, month of vaccination and GP. It was found that the frequency of visits to the GP by the patients with autism in the periods 60 or 180 days before or after vaccination did not differ from that of the controls.

To provide a check on this finding, the researchers also examined the frequency of visits to the GP by the patients who were finally diagnosed with autism during the last 60 and 180 days before the diagnosis, and compared this with the frequency of visits to the GP by the controls during a comparable period. It was found that the patients who ultimately developed autism did visit the GP more often in this period. Autism thus led to an increased frequency of visits to the GP, but MMR vaccination did not.

The authors concluded that it is unlikely that MMR vaccination has any effect on behaviour, but that Taylor and co-workers were right about the clustering of the first expression of concern.[56]

Hypothesis 4: MMR vaccination is associated with a new form of autism

The Immunization Safety Review Committee of the American Institute of Medicine launched a study of the possible existence of a link between vaccination and autism in 2000. This study was concluded in 2001 with a lengthy report.[30] The activities of the Committee included a series of interviews with experts, including Wakefield.

According to Wakefield, the epidemiological studies carried out up to that point had not found any link between vaccination and autism because the researchers had not considered the form of autism linked with MMR vaccination but had used the standard definition of autism – which was not applicable in this case. He claimed that MMR vaccination was linked with a special form of autism, consisting of a combination of behavioural problems and colitis, associated with developmental regression.

This testimony of Wakefield led once again to a series of investigations, now focused on the occurrence of colitis and autism, with or without associated developmental regression, and the possible link with MMR vaccination. It may be mentioned that this topic had already been the subject of a study[57] published in 1998 after the original article by Wakefield and co-workers from 1996. In this

study, Peltola and co-workers selected data on 31 children with colitis after MMR vaccination from the above-mentioned Finnish surveillance system.[57] None of these children developed autism. A second analysis of data from the same system revealed that none of the 352 children diagnosed with autism had been admitted to hospital for colitis.[49]

Fombonne and Chakrabarti likewise showed that the percentage of autistic children with developmental regression was not changed by the introduction of MMR vaccination.[48] They found no link between developmental regression and the occurrence of colitis in the children with autism.

In a study of the period from 1979 to 1998, Taylor and co-workers concluded that the percentage of children with an autistic syndrome combined with colitis or combined with developmental regression was not changed by the introduction of MMR vaccination in 1988.[58] This means that the occurrence of colitis or developmental regression in children with an autistic syndrome was not linked with the MMR vaccination.

Black and co-workers selected a group of vaccinated children with an autistic syndrome and a control group from the UK General Practice Research Database, and examined the occurrence of colitis in the period preceding the diagnosis of autistic syndrome. The control group was examined over a comparable period. The odds ratio for colitis in children with autism compared with the controls was found to be 1.0 (95% confidence interval 0.5-2.2).[59] The authors concluded that children later diagnosed with autistic syndrome did not show more colitis than other children.

3.3 Developments after the first publication

In March 2004, various announcements relating to the publication by Wakefield and his eleven co-workers appeared in the Lancet.[60-63]

Ten of the twelve authors published a *retraction of an interpretation*, in which they stated that while the original publication did not prove a causal relationship between MMR vaccination and autism, it did suggest the possibility of such a relationship. In the light of the many subsequent developments, the authors now jointly retracted their original interpretation of the findings.[60]

Chapter 4

Conclusion

4.1 Conclusion concerning a possible link

The first publication by Wakefield and others about 12 children with behavioural problems and colitis, in which a link with MMR vaccination was suggested[2], led to many further studies. A variety of publications appeared in the succeeding years, ranging from case studies to reports of controlled observational investigations of children – sometimes comprising very large groups – from Denmark, Finland, Japan, the United Kingdom and the United States. The publications are summarised in Table 1. None of these studies found a link between MMR vaccination and autism. A particularly striking investigation was that of Honda and co-workers, who found a rise in the incidence of autism even when the vaccination level fell sharply.[47]

The Committee was unable to find any evidence that MMR vaccination causes, promotes or exacerbates autism. This is in line with the conclusion drawn previously by the WHO and the Institute of Medicine in the United States that there is no evidence of a link between MMR vaccination and autism.[30,64,65]

According to the Institute of Medicine, the hypotheses about the biological mechanism underlying the suggested relationship between MMR vaccination and autism are merely theoretical.[65] The Committee agrees with this conclusion.

Table 1 Studies of the possible link between MMR vaccination and autism, arranged according to the hypothesis tested.

Publication	Type of study	Study population	Results
Hypothesis 1: autism occurs more often in individuals who have been given the MMR vaccine			
Madsen[28]	retrospective cohort study	316 patients with autistic disorder and 422 patients with autistic spectrum disorders from a group of 537 303 children in Denmark	relative risk of autistic disorder 0.92 (0.68-1.24), relative risk of autistic spectrum disorders 0.83 (0.65-1.07)
Hypothesis 2: the increase in the level of MMR vaccination leads to an increase in autism			
Smeeth[44]	matched case control	1294 patients with autism and 4469 controls (UK General Practice Research Database)	odds ratio MMR vaccination and autism 0.86 (0.68 – 1.09).
Dales[42]	observational; time series	Cohorts of schoolchildren in USA, born from 1980 to 1994; 600-1900 children per annum	relative increase in vaccination level 14%; relative increase in autistic disorder 373%
Kaye[43]	observational; time series	Incidence of autism in children up to 12 years old, born from 1988 to 1999 (UK General Practice Research Database)	incidence of autistic disorder rose from 0.3 to 2.1 per 10 000 person years, vaccination level at least 95% throughout entire period
Taylor[45]	observational; time series	498 patients with autistic disorder or atypical autism born from 1979 to 1992 in 8 health districts in London	constant increase in incidence of autistic disorder and atypical autism, not influenced by introduction of MMR vaccine in 1988
Chen[46]	observational; time series	2407 patients with autistic disorder in United Kingdom, born from 1959 to 1993	constant increase in incidence of autistic disorder, not influenced by introduction of MMR vaccine in 1988
Honda[47]	observational; time series	31 426 children born from 1988 to 1996 in Yokohama, Japan	incidence of autism rose while MMR vaccination level fell
Hypothesis 3: there is a temporal relationship between the development of autism and the administration of MMR vaccine			
DeWilde[56]	case control	71 children with autism and 284 controls from United Kingdom	frequency of visits to GP by children ultimately diagnosed with autism in periods round vaccination did not differ from that of controls
Fombonne[48]	case control	3 groups of children with autism from United Kingdom; 2 MMR vaccinated (n=96, n=68), 1 not vaccinated (n=98)	no difference between age of three groups at which parents first expressed concern about autism; no link between developmental regression and occurrence of colitis
Makela[49]	retrospective case series	352 patients with autism, from group of 535 544 vaccinated children in Finland	no clustering in time of hospital admissions for autism after vaccination
Madsen[28]	retrospective cohort study	316 patients with autistic disorder and 422 patients with autistic spectrum disorders from group of 537 303 children in Denmark	no difference between age of vaccinated and unvaccinated children at time of diagnosis; no clustering of diagnosis time after vaccination
Taylor[45]	observational; time series	498 patients with autistic disorder of atypical autism born from 1979 to 1992 in 8 health districts in London, United Kingdom	no difference between age of vaccinated and unvaccinated children at time of diagnosis; clustering of first expression of concern by parents found in 1 of the 12 post-vaccination periods studied

Hypothesis 4: MMR vaccination is associated with a new form of autism			
Black[59]	case control study	96 patients with autism and 449 controls from UK General Practice Research Database, United Kingdom	odds ratio for colitis in children with autism compared with controls 1.0 (0.5-2.2)
Taylor[58]	population study	473 patients with autistic disorder or atypical autism, born from 1979 to 1998 in 5 health districts in London, United Kingdom	percentage of autistic children with colitis or developmental regression showed no change with time
Peltola[57]	retrospective case series	31 patients with colitis, from group of 535 544 vaccinated children in Finland	no patient with colitis became autistic
Makela[49]	retrospective case series	352 patients with autism, from group of 535 544 vaccinated children in Finland	no patient with autism had colitis

4.2 Conclusion concerning the importance of vaccination

The national average percentage of Dutch children who have received MMR vaccinations has been above 95 per cent for years.[66] It may be noted, however, that this percentage shows appreciable variations from one municipality to another and that epidemics have occurred of recent years in people who have not been vaccinated.

In a previous report, the Committee referred to an epidemic of measles among unvaccinated people in the Netherlands in 1999 en 2000.[3,67] Ninety-four per cent of the patients with measles had not been vaccinated, and 157 of the 158 vaccinated patients had not received the second dose of vaccine (in some cases, they would have been due to receive it in the future). There were three fatalities as a result of the epidemic, and 72 patients were admitted to hospital.

In 2004 and 2005, the Netherlands saw outbreaks of rubella.[68] This disease usually has a fairly benign course in children, but infection during pregnancy can lead to abortion, congenital defects or serious disease in the newborn child.[1] The vast majority of the 387 patients had not been vaccinated. Thirty-two infections were reported during pregnancy, leading to 15 congenital rubella infections.68

In their comments accompanying the first article by Wakefield *et al*., Chen and DeStefano warned that this publication could lead to a drop in the vaccination level.[19] Such a drop could then lead to a rise in the incidence of the disease the vaccination was designed to protect against.

The Committee would like to stress the importance of this warning, which is borne out by the fact that such effects have already been observed several times.

For example, a publication on the side effects of vaccination against whooping cough in the 1970s was followed by a drop in the vaccination level against whooping cough in the United Kingdom, and a rise in the number of patients.[69] The vaccination level against whooping cough also fell strongly in other countries, causing the incidence to be a hundred times higher than in the countries where this drop in the vaccination level was not observed.[70]

Outbreaks of measles have been occurring to an increasing extent in the United Kingdom of recent years, also linked to a low vaccination level.[71] In Japan, concern about the safety of vaccination against measles and the resulting strong drop in vaccination level of recent years have led to more than 100 000 cases of measles per annum, with an estimated number of fatalities of between fifty and a hundred.[72]

A drop in the vaccination level in the Netherlands would also lead to an increase in mumps, measles or rubella here, and hence to increased morbidity and mortality that could have been prevented by vaccination.

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A The Committee

Annex

Annex **A**

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