National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Human papillomavirus vaccination catch-up campaign in 2009 for girls born in 1993 to 1996 in the Netherlands

Results of the post-marketing safety surveillance

Report 210012001/2011

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Colophon

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Abstract

Human papillomavirus vaccination catch-up campaign in 2009 for girls born in 1993 to 1996 in the Netherlands
Results of the post-marketing safety surveillance

In 2009, no serious adverse events were reported after vaccination against human papillomavirus (HPV) that were considered causally related to the vaccination. Research on adverse events in this year implies that the HPV vaccination catch-up campaign has been a safe intervention on the short-term. Girls experienced frequently pain at the injection site and myalgia, but mostly mild and all were transient.

Vaccination against HPV, the virus that can cause cervical cancer, was newly introduced in 2009 in the Netherlands. In 2009, girls born in 1993 to 1996 were invited for vaccination. From 2010, yearly 12-year-old girls were invited. Vaccination includes three doses, administered on mass vaccination locations. In total 558,226 doses were administered in 2009.

In intensified safety surveillance, all immediate occurring adverse events on locations of mass vaccination were registered. Besides that, spontaneous reports were collected through the enhanced passive surveillance system. Furthermore, a questionnaire study was performed on the tolerability of the vaccine.

The reporting rate of immediate occurring adverse events on locations of mass vaccination was 27.1/10,000 administered doses. Most frequently reported was presyncope and syncope (62.1%). The reporting rate of spontaneous reports was 11.6/10,000 administered doses. In 13.4% it concerned major adverse events, for instance fainting, migraine, and convulsions. Of these major adverse events, 75.6% were assessed causally related to the vaccination.

In the survey on tolerability, 85% of the girls, on average after the three successive doses, reported local reactions, such as pain at the injection site or reduced use of the arm. Of these reactions 16% were classified as pronounced. Systemic adverse events, for instance myalgia, fatigue, or headache, were experienced by 83% of the girls on average.

Key words:
adverse events following immunisation, safety surveillance, tolerability, HPV vaccination, National Immunisation Programme, human papillomavirus

Rapport in het kort

Humaan papillomavirus vaccinatiecampagne voor 13-16-jarige meisjes in 2009 in Nederland
Resultaten van de postmarketing veiligheidsbewaking

In 2009 zijn over de humaan papillomavirus (HPV) vaccinatie inhaalcampagne geen ernstige verschijnselen na vaccinatie gemeld die door het vaccin zijn veroorzaakt. Het vaccin kan daardoor op de korte termijn als veilig worden beoordeeld. Dit blijkt uit onderzoek naar de mogelijke bijwerkingen van het HPV vaccin van dat jaar. De meisjes hebben veelvuldig verschijnselen als pijn in de arm en spierpijn gemeld, maar deze bleken over het algemeen mild en kortdurend.

In Nederland is in 2009 de vaccinatie tegen het HPV geïntroduceerd, het virus dat baarmoederhalskanker kan veroorzaken. In 2009 zijn de 13- tot en met 16-jarige meisjes ingeënt. Vanaf 2010 worden jaarlijks 12-jarige meisjes gevaccineerd. Het schema bestaat uit drie prikken, die de meisjes op grootschalige locaties krijgen toegediend. In 2009 zijn in totaal 558.226 doses van dit vaccin toegediend.

In het onderzoek zijn de mogelijke bijwerkingen geregistreerd die op de vaccinatielocatie optraden. Daarnaast zijn de zogeheten spontane meldingen voor dit vaccin verzameld vanuit het reguliere systeem voor meldingen van mogelijke bijwerkingen van vaccinaties. Tot slot is onderzocht hoe de meisjes het vaccin verdroegen door hen een vragenlijst over mogelijke bijwerkingen te laten invullen.

Bij 27 per 10.000 toegediende doses zijn kort na de vaccinatie verschijnselen opgetreden. (Bijna) Flauwvallen kwam hierbij het vaakst voor (62,1%). Spontane meldingen zijn in 11,6 keer per 10.000 toegediende doses gemeld. In 13,4% ging het om een heftige gebeurtenis, zoals flauwvallen, migraine en stuipen, als mogelijke bijwerking van het vaccin. Hiervan werd bij 75,6% een oorzakelijk verband met de vaccinatie vastgesteld.

In het onderzoek naar verdraagbaarheid rapporteerde 85% van de meisjes over de drie prikken gemiddeld een reactie rond de prikplaats, zoals pijn of verminderd gebruik van de arm. Hiervan classificeerde gemiddeld 16% van de melders de reactie als heftig. Verschijnselen als spierpijn, moeheid of hoofdpijn, kwamen voor bij gemiddeld 83% van de deelnemers.

Trefwoorden:
bijwerkingen na vaccinatie, veiligheidsbewaking, HPV vaccinatie, Rijksvaccinatieprogramma, humaan papillomavirus

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Summary

In 2008, a decision was taken by the Ministry of Health, Welfare and Sport in the Netherlands to implement vaccination against human papillomavirus (HPV). In 2009, a catch-up campaign was organised for girls born in 1993 to 1996 (13-to-16-year-old). The bivalent HPV-16/18 vaccine was used for the campaign and was administered in three doses, at intervals of 0, 1 and 6 months. The introduction of a new vaccine as well as the new target group stressed both the importance of an intensive post-marketing surveillance.

Intensive surveillance on the safety of the vaccine was performed by means of surveillance of immediate occurring adverse events (AEs) on locations of mass vaccination, the enhanced passive surveillance, and a survey on tolerability. For the surveillance of immediate occurring AEs on location of mass vaccination, report forms were distributed among all locations. Municipal Health Service workers were asked to report all immediate occurring events. The enhanced passive surveillance included spontaneous reports of AEs. In the survey on tolerability, participating girls filled in a web-based questionnaire on local reactions and systemic AEs.

We received 1107 reports of immediate occurring AEs on locations of mass vaccination on 408,662 administered doses. This results in a reporting rate of 27.1/10,000 administered doses. In 688 cases (62.1%) it concerned presyncope and syncope, in 322 cases (29.1%) other vasovagal symptoms, in 53 cases (4.8%) dyspnoea and in 14 cases (1.2%) skin symptoms. Twelve girls got assistance from ambulance personnel and nine visited a general practitioner.

On a total of 558,226 administered doses, we received 647 spontaneous reports on AEs, resulting in a reporting rate of 11.6/10,000 doses. Most AEs were reported following the first dose (77.8%). In 86.6% of the reports the event was assessed as ‘minor’. ‘Major’ AEs occurred in 13.4%. Of the minor events 60.0% were considered as adverse reactions and of the major events 75.6%. In 16.2% of the reports it concerned predominant local reactions, in 11.4% general skin symptoms, and in 8.6% presyncope and syncope. The general practitioner was contacted in 30.6% of the cases and 6.6% went to a hospital.

In the survey on tolerability 4248 girls participated and returned one or more questionnaires after vaccination. Local reactions were reported by 92.1% of the girls after the first dose, 79.4% after the second dose, and 83.3% after the third dose. Of these local reactions 22.1%, 12.1%, and 14.8% were classified as pronounced, respectively. Pain at the injection site was the most frequently reported local reaction. Systemic AEs were reported in 91.7%, 78.7%, and 78.4% of the girls, respectively. Myalgia was the most often reported. The frequency of reported AEs was dependent on the dose and the age of the girl, with lower proportions after the second and third dose and for younger age. Four girls visited the emergency room within 7 days after vaccination, of which in only one case a relation to the vaccination was possible.

After vaccination of girls 13 to 16 years of age with the bivalent HPV vaccine, the reporting rate of immediate occurring AEs on locations of mass vaccination and spontaneous reports was higher than in several other countries. The incidence rate of presyncope and syncope was comparable to the mass vaccination campaign against Meningococcal C in 2002 in the Netherlands. In the survey on tolerability, girls reported high proportions of local reactions and systemic AEs. This is comparable with results from several clinical trials of the bivalent HPV vaccine and after diphtheria, tetanus, and inactivated polio vaccination in the Netherlands. Overall, we received no serious AEs with assessed causality to the vaccination. Results are being communicated to health care professionals and the public to help increase confidence in HPV vaccination and in vaccination generally.

1 Introduction

In April 2008, the Dutch Health Council (DHC) published a report on vaccination against human papillomavirus (HPV). They advised in favour of introduction of the HPV vaccine in the National Immunisation Programme (NIP), because the vaccine can protect against approximately 70% of all cases of cervical cancer.[1] Subsequently, a decision was taken by the Ministry of Health, Welfare and Sport to include HPV vaccination into the Dutch NIP. The DHC stated that the vaccine should be provided to all girls aged 13 to 16 years (birth cohorts 1993 to 1996) in a catch-up campaign. In addition to this catch-up campaign, this vaccination would be incorporated in the realm of the vaccination programme on the age of 12 years (girls born in 1997 and later). Because the HPV vaccine has been on the market since 2007, rare AEs of the vaccine and the effectiveness on long term are not known. This can only be detected by post-marketing surveillance. Therefore, it was recommended that an intensified monitoring system accompanied the introduction of HPV vaccination in the NIP, for all aspects of the virus, the disease and the vaccine.

An intensive post-marketing surveillance is critical for following and monitoring the campaign as well as for the consequences such as AEs, public opinion, and response related to the vaccine and the (media) campaign. Several organisations were involved in the process of introducing HPV vaccination into the NIP as well as the catch-up campaign. Guidance was provided on several aspects and included support from the Municipal Health Services Netherlands (MHS-NL) with administering and supplying the vaccine. In addition a broad communication campaign targeting public information was started and included websites, newsletters for health care professionals, and a brochure for professionals of the Ministry of Health, Welfare and Sport as well as information for parents and girls.[2-4]
There was a national helpdesk (‘Postbus 51’) telephone number available for the general public (besides the own services from the Municipal Health Services (MHS)). Furthermore, a telephone information service of the National Institute for Public Health and the Environment (RIVM) for consultation and advice for health care professionals involved was in place.

In this report the human papillomavirus and the impact of vaccination is briefly discussed in chapter 2. Chapter 3 describes the organisation and scope of the national HPV vaccination campaign. Furthermore, the methods and results of the three different aspects of safety surveillance during the HPV vaccination catch-up campaign are described in chapters 4 and 5. Firstly, the recording of immediate occurring AEs on locations of mass vaccination is presented. Secondly, the reporting through the enhanced passive safety surveillance system is described, and thirdly, the survey on tolerability of the vaccine will be discussed. Discussion, conclusions and recommendations follow in chapters 6 and 7.

2 Cervical cancer by human papillomavirus

Cervical cancer is the second most frequently occurring cancer in women worldwide and the fifth most frequently occurring in women in the Netherlands.[5-6] Infection with HPV is a necessary condition for cervical cancer.[5]

2.1 Infection with HPV

HPV's are a family of more than 120 known viruses.[7] They are distinctly small (55 nm) non enveloped icosahedrons with circular double-stranded DNA genomes of about 8000 base pairs, encoding 8 genes.[8] More than 40 types are able to infect the human anogenital tract, of which 15 types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) were classified as high risk for development of cervical and other forms of cancer. Three types of HPV (26, 53, and 66) were classified as probable high risk, 12 types (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CCP6108) as low risk, and 3 types (34, 57, and 83) are undetermined.[9] The most common types found in cervical cancers are HPV-16 and HPV-18.[10]

HPV's must be introduced into a break, tear or abrasion in the outer layer of the skin. The genital HPV's enter through micro fissures during sexual intercourse.[11] After the differentiation of an infected cell, the activity of the genes E6 and E7 increase. An increased activity of E7 results in the activation of the biochemical machinery of the host cell, responsible for duplication of the DNA, which is necessary for replication of the viral DNA. Subsequently, E6 activity prevents against self destruction of the cells by blocking their own killing mechanism. Released virus particles assemble in the outer layers of the skin.

A well documented risk factor for HPV infection is an increasing number of sex partners during a lifetime. Several other possible risk factors such as smoking and oral contraceptives were hard to investigate and therefore inconclusive on relationship with HPV infection.[5,7]

Infection can be cleared or contained by a healthy immune response. Even high-risk types can be cleared spontaneously, but it appears that for HPV-16 it takes longer to be cleared compared with other types. More than half of the women no longer had detectable HPV DNA after 12 months. Several cohort studies indicated that only some women were repeatedly positive for a given HPV type.[12-13] A common finding was the presence of multiple HPV types per individual but the role of such multiple HPV infections on clearance or persistence is not certain.[5,7]

Based on various reports it can be stated that there is a strong relation between persistent HPV infection and the development of precancerous cervical lesions and invasive cancer.[14-16] However, there still is no consensus on the definition of the timeframe that can be called 'persistent'.[7] Furthermore, HPV infection itself is not a sufficient cause for cervical cancer. Another important factor is the immune status of the infected person. Cervical cancer is viewed as a rare consequence of

a very common HPV infection.[17-18] When an HPV infection persists for years on end, it invades the cervical tissue cells and transfers genetic material, which leads to abnormal changes in the cell. Histological changes in the tissue on the passage of the cervix to the uterus can degenerate into precancerous lesions as cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SILs) and eventually into cervical cancer - usually over 12 to 15 years.[18]

Cervical cancer or precancerous lesions are diagnosed in most cases with a papanicolaou test with subsequent biopsy. The papanicolaou test, or short Pap test or smear, can detect abnormal cervical cells before they have a chance to develop into cervical cancer. It can help detect cervical cancer while it is still in the early stages and more easy to treat. A Pap test is one of the paramount screening methods for detecting abnormal cervical cells and cervical cancer. This was one of the reasons the DHC recommended to sustain the population screening for cervical cancer. After the Pap smear indicates possible abnormal cervical cells biopsy is performed to confirm the diagnosis.[19]

2.2 Epidemiology of cervical cancer

HPV infections are the most common sexually transmitted infections worldwide.[7] Various epidemiologic studies have shown that the prevalence of HPV infection is highest among young sexually active women.[5,7]

In the Netherlands 600 to 700 patients are annually diagnosed with cervical cancer and the last 10 years 200 to 250 women per year died because of cervical cancer. Incidence of cervical cancer shows a peak around the age of 35.[20,21]

The number of new cases of cervical cancer has decreased with 32% in the period 1989-2003, and in the period 1980-2005 the number of women who died due to cervical cancer decreased with 51%. This decrease in new cases and deaths is probably due to the introduction of screening of Dutch women aged between 30 and 60 years to cervical cancer in 1976. The prevalence of cervical cancer in the Netherlands increased with approximately 4% per year for women aged 35 to 64 years because of decreasing mortality due to cervical cancer.[17]

Since HPV infections may lead to cervical cancer and cervical cancer needs decennia to develop, a decrease in the number (incidence) of cervical cancer can only be detected on the long term (approximately 20 years or more). This was the reason why the DHC advised to incorporate long term effect studies of HPV vaccination in the programme to underpin the rationale for introduction of HPV vaccination. Also DHC stated that it was important to investigate which type of HPV is involved in the diagnosed cervical cancers to detect type-switching or type-replacement.[1]

2.3 Prevention of cervical cancer

Since 1976, screening of cervical cancer is provided by the government. Women aged 30 to 60 years are invited to take a cervical smear every five years to detect cervical cancer and precancerous lesions. Every year, approximately 800,000 women receive an invitation for the

screening and about 66% of these women participate. With this coverage, screening prevents about 200 deaths yearly and reduces the life time incidence of women for cervical cancer from 15/1000 to 6/1000.[22]

The HPV types 16 and 18 are responsible for approximately 70% of the cervical cancer cases. Diminishing the occurrence of (high-risk) HPV infections should lead to prevention of cervical cancer. Two HPV vaccines has been registered in the Netherlands: Gardasil® (Merck and Co.), a quadrivalent vaccine that protects against HPV types 6, 11, 16 and 18 and Cervarix® (GlaxoSmithKline), a bivalent vaccine protecting against the HPV types 16 and 18.[1,20]

After introduction of the quadrivalent HPV vaccine in 2006 several national vaccination programmes were started, in the United Kingdom, in Canada, in Australia, and in other countries. The Netherlands followed shortly after. Besides the screening for cervical cancer which was already ongoing, the choice for a nationwide vaccination campaign was stipulated by additionally preventing hundreds of cases of cervical cancer and about 100 deaths yearly.[1]

The Ministry of Health, Welfare and Sport decided to use the bivalent HPV vaccine. This vaccine had the most favourable cost-benefit balance in the European tender. A single vaccination is insufficient to guarantee protection against all HPV triggered lesions which can cause cervical cancer. To induce optimal protection, three vaccinations must be administered within a year. According to recommendation, the optimal vaccination schedule would be at intervals of 0, 1, 6 months.[1,20,23]

HPV is sexually transmitted and therefore occurs in most cases shortly after the onset of sexual activity. Therefore, it is necessary to offer vaccination before girls become sexually active. The DHC stated that 12-years-old would be an appropriate age to introduce the vaccine, because most girls have not had sex yet. Shifting to an older age would lead to strong increase of the costs weighted against the benefits, since girls may already have been infected.[1,20,23]

Different studies show a high efficacy and good safety profile of the bivalent HPV vaccine [24-27], but the effectiveness and the safety of the vaccine for large-scale application and on a longer term were not clear at the time of introduction. Much longer follow-up is necessary as is also advised by the DHC.[1,20]

3 National human papillomavirus vaccination campaign

Following the advice of the DHC (April 2008), a decision was taken by the Dutch Ministry of Health, Welfare and Sport to incorporate HPV vaccination in the realm of the NIP. From March 2010, girls born in 1997 were offered HPV vaccination under the NIP. Girls born in later years receive an invitation for vaccination in the upcoming years. Older girls to the age of 16 years (birth cohorts 1993 to 1996) received the vaccination in a national catch-up campaign which started in March 2009.[4,23]

The implementation of the HPV vaccination introduced a new vaccine-moment into the NIP for 12-year-old girls. Initially, after the summer holidays of 2009 the NIP would start with the vaccination of 12-year-old girls. However, due to an outbreak of pandemic influenza A(H1N1) and the foreseen logistic pressure on the MHS when vaccination against pandemic influenza A(H1N1) was performed, this introduction into the NIP was postponed to March 2010. The third vaccination for the catch-up campaign in September 2009 was not postponed.[28]

3.1 Organisation of the campaign

The whole campaign was designed and coordinated by the HPV-project team with representatives from several organisations, to guarantee cooperation of all organisations involved. Additionally a research platform was formed under the chairmanship of the Epidemiology and Surveillance unit of the Centre for Infectious Disease Control (CIb) of the RIVM, to develop and perform the surveillance and evaluation of the HPV vaccination campaign. Regarding to safety, this concerned intensive monitoring of vaccination coverage, safety of the vaccine, efficacy of vaccination, and prevalence of HPV types.[23,29]

The information for the public and proactive media coverage were developed by the RIVM as well as the invitations for vaccination and the registration of the vaccinations. National substantive and logistical directives were formulated. Furthermore, a national slogan with logo was developed to reach uniformity. During the campaign, weekly newsletters were spread digitally to all participating organisations.

3.2 Regional implementation of the campaign

Twenty-nine MHS performed the campaign under the guidance of MHS-NL and CIb, including the regional coordination of the five RIVM-CRP offices (Regional Coordination Programmes). Regional agreements with other parties were made, such as District Health Care, Red Cross, municipal authorities etc. MHS-teams were responsible for the entire logistic organisation and the RIVM for addressing all girls concerned.

Standard invitation sets were sent with an information leaflet for teenage girls and their parents (Appendix 1), including bar code and recall and registration card with an accompanying letter of the MHS (Appendix 2). In dialogue with the regional MHS a tight distribution schedule was established to insure availability of vaccine. The regional MHS also monitored the cold chain guidelines.[29]

3.3 Vaccine

A bivalent HPV L1 virus-like particle (VLP) vaccine against HPV types 16 and 18 (Cervarix®, GlaxoSmithKline) was used for the campaign. Three vaccinations must be administered at intervals of 0, 1, and 6 months to induce optimal protection.[23]

Part of this vaccine is a new adjuvant, called AS04, comprising aluminium salt and the immunostimulant 3-O-desacyl-4'-monophosphoryl lipid A (MPL), resulting in higher antibody levels and production of memory cells.[30] This immune response was assessed to persist for up to 20 years.[31]

The vaccine showed an efficacy in HPV-naïve women of 100% for HPV types 16 and 18 related persistent infections and CIN grade 2 and above up to 8.4 years after vaccination.[32] Cross-protection has been observed against the HPV types 31 and 45.[25] Different studies showed that the vaccine is generally safe for different age categories and female populations.[25]

3.4 Substantive support and information

There were several ways to get information about the campaign. For health care professionals there was a website especially introduced for this vaccination (www.rivm.nl/hpv), a digital newsletter and a specially designed 'toolkit' was available via RIVM education centre.[33] Furthermore, a telephone service for consultation and advice for health care professionals was available. The target population was informed through a campaign website with incorporation of the slogan (www.prikenbescherm.nl)[2], besides the already mentioned letter and leaflet they received at home and the 'Postbus 51' telephone number.

3.5 Safety surveillance

The World Health Organisation (WHO) provides directives on how to organise the safety surveillance of vaccination programmes.[34-36] Vaccinations differ on several points from 'ordinary' or 'regular' medicines, because they are biological pharmaceuticals that have inherent batch differences and aim at a permanent effect (Diagram 1). The preventive character of the intervention, the administration to healthy girls, a certain degree of moral coercion as well as the public health aspect, and the lack of alternative interventions among other things makes that particular demands must be enforced on the safety surveillance of these national vaccination programmes.

Diagram 1 Particular aspects of HPV vaccination campaign with extra requirements safety surveillance

· Preventive intervention · Aimed at individual protection · Healthy (young) girls · Programmatic use · Cost free with strong insistence to vaccinate the target population · Public health importance · Vaccine newly introduced on the market · No know effects on long term · No good alternatives · Under attack from critical groups of public apprehension

Especially vaccination programmes concerning a new vaccine and in a new target group require specific guarding or security. A public and political insistence to the campaign can easily turn from broad support into an 'anti' movement if particular or unexpected AEs are identified or even suspected. By then, it already does not matter whether there are real concerns or only perceptions. This can damage the confidence not only where the HPV vaccine is concerned, but also in the immunisation programme in general with particularly serious consequences for (Dutch) children. A good example is the disarray in France during the national Hepatitis B vaccination campaign.[37-38] Therefore it is necessary to proactively study the safety aspects of the vaccine used. For this reason, a survey on the tolerability of HPV vaccination was performed in this campaign and the monitoring of immediate occurring AEs during mass vaccination sessions has been included, besides the enhanced passive surveillance. This opens the possibility for rapid action if necessary.

As already stated in the introduction, three major actions to guide the post-marketing safety surveillance on the short-term were used. The recording of immediate occurring AEs, so-called 'acute incidents', on locations of mass vaccinations are described. Furthermore, the enhanced spontaneous reports are presented. And lastly, results of the questionnaire study on tolerability that took place at six vaccination locations in the central of the Netherlands are shown. In addition to the monitoring of these short-term AEs, surveillance on the AEs on the longer term is also in process. Hereby, we assess age and sex specific background incidence rates of several immune mediated disorders, followed by linking studies to monitor a possible association between HPV-vaccine and each specific disease.

4 Methods regarding safety surveillance of the HPV vaccination campaign

The safety surveillance of the NIP in the Netherlands consists of an enhanced passive reporting system for AEs following immunisation (AEFI), supplemented with other systematic studies. Since the HPV vaccination campaign was newly introduced in the Netherlands and concerning a new age group in the NIP, the safety surveillance was intensified to get a more complete view on AEs, including mild symptoms. It consisted of three different surveillance methods, already mentioned in chapter 3. This chapter will describe the methodology of these three methods.

4.1 Immediate occurring adverse events on locations of mass vaccination

Among the immediate occurring AEs presyncope and syncope was of special importance. Syncope can lead to trauma, sometimes resulting in a life threatening event. Furthermore, syncope sometimes goes together with symptoms like jerking or convulsion-like movements, possibly leading to incorrect diagnosis and unnecessary interventions. Furthermore, anaphylaxis needs special attention. This is a very rare adverse event, with estimated incidence rates of 1-10 per 1,000,000 depending on type of vaccine and used case definitions.[39]
A report form was available especially for the monitoring of these immediate occurring AEs during the mass vaccination sessions of the HPV vaccination campaign (see section 4.1.1). Report forms were distributed among all locations of mass vaccination and MHS staff were asked to report all immediate occurred AEs. The filled in forms were sent to the RIVM. MHS could keep a copy for their own administration and follow-up.

4.1.1 Report forms

There were two separate report forms (Appendix 3). One for the registration of individual immediate occurring AEs, containing information of the patient, symptoms, interval, and duration of symptoms, injury and medical intervention. The other form was designed to collect information on the total number of reported immediate occurring AEs, together with the total number of administered vaccines per mass vaccination session and a description of the local circumstances.

4.1.2 Analysis

For presyncope and syncope, other vasovagal symptoms, jerking, vomiting, dyspnoea or skin symptoms, incidence rates with 95% confidence intervals (CI) were calculated after all three doses. Pre-syncope was defined as pallor combined with one additional symptom out of dizziness, sweating, nausea, vomiting, and fits. When pallor was not recorded, three symptoms of the preceding list needed to be present. Furthermore, injury and the need for medical intervention with the type of interventions were analysed.

4.2 The enhanced passive reporting system

4.2.1 Post-vaccination events

Undesirable phenomena after a vaccination are not necessarily caused by the vaccination itself. For that reason the neutral term adverse event (AE) or Adverse Event Following Immunisation (AEFI) was used. This term doesn't indicate whether or not there is a causal relation between vaccination and the occurring phenomenon.
The term report or notification in this report is synonymous to the term adverse event.

4.2.2 Reporting routes

AEFI could be reported through the telephone service for consultation and advice for health care professionals. In case of reporting by telephone, a special report form was filled in by the medical expert, answering the phone. Furthermore, special report forms for written notifications could be downloaded from the website and be posted to RIVM. Digital reporting was possible also.

4.2.3 Reporting criteria

AEs are subdivided in several categories based on underlying mechanisms after validation.[40] This is considered to be very useful because it can help to prevent side effects, address contra-indications, and to take preventive treatments or precautions (Diagram 2). This subdivision of reports is irrespective of the judgement concerning the causal relation.

Diagram 2 Origin / subdivision of AEs by mechanism

a- Vaccine or vaccination intrinsic reactions	Are caused by vaccine constituents or by vaccination; examples are fever, local inflammation and crying.
b- Vaccine or vaccination potentiated events	Are brought about in children with a special predisposition or risk factor. For instance, febrile convulsions.
c- Programmatic errors or administering errors	Are due to faulty procedures: for example the use of non-sterile materials. Loss of effectiveness due to faulty procedures may also be seen as adverse event.
d- Chance occurrences or coincidental events	Have temporal relationships with the vaccination but no causal relation. These events are of course most variable and tend to be age-specific common events.

Because the enhanced passive surveillance system is in place at RIVM since 1962 and reporting rates are stable and high, reporting criteria are well known to all professionals involved in the NIP (Diagram 3).[41] The reporting criteria are spacious to get a better signal detection.

Diagram 3 Reporting criteria for AEs under the HPV vaccination campaign

- Serious events
- Uncommon events
- Symptoms affecting subsequent vaccinations
- Symptoms leading to public anxiety or concern

Irrespective of the causal relation

Of special importance are the cluster reports (various children). This concerns coincident AEs with similar nature, place and time. These cluster reports are a particular indicator for procedure errors or faulty in product or supply. Even when report entries are completely separated, one should always be aware of possible cluster reports.

4.2.4 Classifying of adverse events

After verification and completion of data, a (working) diagnosis was made. If symptoms do not fulfil the criteria for a specific diagnosis, the working diagnosis was made based on the most important symptoms. Also the severity of the event, the duration of the symptoms and the time interval with the vaccination were determined as precisely as possible. Case definitions were used for the most common AEs and current medical standards were used for other diagnoses.

Some categories are subdivided in minor and major according to the severity of symptoms. Major is not the same as medically serious or severe, but this group does contain the severe events. Definitions for Serious Adverse Events (SAE) by European Medicines Agency (EMA) and International Conference on Harmonisation (ICH) differ from the criteria for major in this report.

Events reported after vaccinations included in the NIP:
Local (inflammatory) symptoms
Events were booked here if accompanying systemic symptoms do not prevail. Events were booked as minor in case of (atypical) symptoms, limited in size and/or duration. Major events were extensive and/or prolonged and include abscess or erysipelas.

General illness
This category includes all events that cannot be categorised elsewhere. Fever associated with convulsions or as part of another specific event is not listed here separately. Crying as part of discoloured legs syndrome is not booked here separately. Symptoms like crying < 3 hours, fever < 40.5 °C, irritability, pallor, feeding/eating and sleeping problems, mild infections, etcetera were booked as minor events. Major events included fever ≥ 40.5 ºC, autism, diabetes, idiopathic thrombocytopenic purpura (ITP), severe infections, etcetera.

Persistent screaming
This major event was defined as (sudden) screaming, non-consolable and lasting for three hours or more. Persistent screaming as part of discoloured legs syndrome was not booked here separately.

General skin symptoms
Symptoms booked here were not part of general (rash) illness and not restricted to the reaction site. The subdivision in minor and major was made according to severity.

Discoloured legs or arms
Events in this category were classified as major and defined as even or patchy discolouration of the leg(s)/arm(s) and/or leg/arm petechiae, with or without swelling. Extensive local reactions were not included.

Faints
Symptoms listed here were not explicable as post-ictal state or part of another disease entity. Three different diagnoses were included, all considered major.
- Collapse: sudden pallor, loss of muscle tone and consciousness, also called Hypotonic Hyporesponsive Episode, mostly occurring in young infants.
- Breath holding spell: fierce crying, followed by breath holding and accompanied with no or just a short period of pallor/cyanosis.
- Fainting: sudden onset of pallor, sometimes with limpness and accompanied by vasomotor symptoms, occurring in older children.

Fits
Three different diagnoses were included in this category, all considered major.
- Convulsions: were discriminated in non-febrile and febrile convulsions and include all episodes with tonic and/or clonic muscle spasms and loss of consciousness. Simple febrile seizures last ≤ 15 minutes. Complex febrile seizures last > 15 minutes recur within 24 hours or have asymmetrical spasms.
- Epilepsy: definite epileptic fits or epilepsy.
- Atypical attack: paroxysmal occurrence, not fully meeting criteria for collapse or convulsion.

Encephalitis /encephalopathy
Events booked here were considered major. A child < 24 months with encephalopathy has loss of consciousness for ≥ 24 hours. Children > 24 months have at least two out of three criteria: change in mental state, decrease in consciousness, seizures. In case of encephalitis symptoms were accompanied by inflammatory signs. Symptoms were not explained as post-ictal state or intoxication.

Anaphylactic shock
These major events must be in close temporal relation with intake of an allergen, type I allergic mechanism was involved. In case of anaphylactic shock there was circulatory insufficiency with hypotension and life threatening hypoperfusion of vital organs with or without laryngeal oedema or bronchospasm.

Death
This category contains any death following immunisation. Preceding diseases or underlying disorders were not booked separately. All events were considered major.

The normally used classifications have been especially tailored to the vaccinations of the NIP and the possible side effects, in particular for young children. Therefore 'persistent screaming' or breath holding spell will almost not occur within the HPV vaccination campaign in contrast to fainting, which will probably occur more often than within the general NIP.[42-44]

4.2.5 Causality assessment

Once it was clear what exactly happened and when, and predisposing factors, underlying disease and circumstances had been established, causality would be assessed. This required adequate knowledge of epidemiology, child health, immunology, vaccinology, aetiology and differential diagnoses in paediatrics (Diagram 4).

Diagram 4 Points of consideration in appraisals of causality of AEFI

- Diagnosis with severity and duration - Time interval - Biological plausibility - Specificity of symptoms - Indications for other causes - Proof for vaccine causation - Underlying illness or concomitant health problems

The nature of the vaccine and its constituents determine which side effects it may have and after how much time they occur. For different (nature of) side effects different time limits/risk windows may be applied. Adverse reactions, due to a direct effect of inactivated vaccines like HPV vaccine, usually occur within 24 hours after vaccination and are of short duration. For AEs with an immune mediated mechanism the interval with the vaccination is usually much longer in order to make a causal relation plausible.[45-48]
Causal relation would then be appraised on the basis of a checklist, resulting in an indication of the probability/likelihood that the vaccine is indeed the cause of the event. This list is not (to be) used as an algorithm although there are rules and limits for each point of consideration (Diagram 5). Causality was classified by one of five different categories.

Diagram 5 Criteria for causality categorisation of AEFI

1-Certain	Involvement of vaccine/vaccination is conclusive through laboratory proof or mono-specificity of the symptoms and a proper time interval.
2-Probable	Involvement of vaccine is acceptable with high biologic plausibility and fitting interval without indication of other causes.
3-Possible	Involvement of vaccine is conceivable, because of the interval and the biologic plausibility but other cause are as well plausible/possible.
4-Improbable	Other causes are established or plausible with the given interval and diagnosis.
5-Unclassifiable	The data are insufficient for diagnosis and/or causality assessment.

4.2.6 Expert panel

An expert panel re-evaluates the formal written assessments by the RIVM. The group consists of specialists on paediatrics, neurology, immunology, pharmacovigilance, microbiology, and epidemiology and is set up by RIVM to promote broad scientific discussion on reported AEs.

4.2.7 Analysis

All notifications were coded in a predefined uniform way. Strict criteria for case definitions and causality assessment were used. Reporting rates were calculated using data from the national immunisation registry. This registry contains name, sex, address, and birth date of all children up till 18 years of age. The database is linked with the municipal population register and is updated regularly or on line for birth, death, and migration. All administered vaccinations are entered in the database on individual level. Therefore, denominator-information is available.

4.3 Survey on tolerability

During the catch-up campaign a survey was performed regarding the tolerability of the HPV vaccine on six locations of mass vaccination at the central of the Netherlands. During the first vaccination session a total of 6000 girls, including 1500 from each birth cohort (1993 to 1996), were approached to fill in a web-based questionnaire to measure frequent occurring AEs. A week after each of the three doses they received the link to the questionnaire by e-mail. If the questionnaire was not returned in 1.5 weeks, a reminder was sent by email.

4.3.1 Questionnaire

The survey contained different kinds of questions (Appendix 4). Girls were asked about date of birth, date and location of vaccination, underlying illness (eczema, allergy, asthma, hay fever, and diabetes mellitus) and sickness during the week before vaccination (headache, cold, or flu) or at the time of vaccination (cold or flu). The questionnaire contained questions about AEs within seven days after immunisation. Girls were asked to record local reactions (swelling, redness, pain at the injection site, swelling in armpit or reduced use of the arm) and systemic AEs (fever, listlessness, crying, cold, coughing, dyspnoea, fatigue, sleeping problems, nausea, vomiting, diarrhoea, abdominal pain, headache, dizziness, fainting, myalgia, joint pain, muscle contractions, sweating, rash, itching or other unsolicited symptoms). The severity of local reactions was graded on a four-point scale, for swelling and redness: none, less than 2.5 cm (comparable to the size of a 2-Euro coin), 2.5 to 5 cm and more than 5 cm, and for pain at the injection site, swelling in armpit and reduced use of the arm: none, mild, moderate or pronounced. Fever was reported as continuous, but it was presented as ≥ 38 °C, according to the criteria of the Brighton Collaboration.[49] Other systemic AEs were dichotomized (yes/no). Time interval and duration of symptoms were collected, as well as the use of analgesics, other medical intervention, absence from school, sport or other activities, or a parent's or guardian's absence from work as the vaccinated girl's caretaker.

4.3.2 Sample size

To make a reliable estimate on the frequency of short-term AEs after vaccination against HPV we estimated that 1000 questionnaires should be distributed for each birth cohort (prevalence = 0.46, confidence level = 95%, absolute precision = 5%, response = 50%, percentage lost to follow-up during the study = 20%).
During the catch up campaign, 500 extra questionnaires per birth cohort were distributed to ensure enough participants for each birth cohort, because the extra effort was relative small.

4.3.3 Analysis

Proportions of local reactions and systemic AEs within seven days after immunisation were analysed for each of the three doses with a corresponding 95% confidence interval (CI) and median duration. This was done for all participants on each round (girls who returned questionnaire) and for the girls who returned all three questionnaires (‘complete responders’). In addition, proportions were calculated for local reactions that occurred within 72 hours and systemic AEs that occurred within 24 hours after immunisation to estimate the causality rate of AEs for the HPV vaccination.
Furthermore, frequencies of underlying illness, sickness during the week before or at the time of vaccination, the use of analgesics, other medical intervention and absency were calculated with 95% confidence interval and median duration if applicable. Trends in all variables mentioned above between birth cohorts were analysed using the Chi-square test for trend. Differences in frequencies of AEs between vaccination locations were tested with the Chi-square test.
Using generalized linear mixed models (GLMM) we analysed the variation (with standard error) in the risk for AEs corrected for birth cohort and dose between participants. Differences between doses, corrected for birth cohort and variation between participants, were analysed and presented as odds ratios (OR). Differences between birth cohorts, corrected for dose and variation between participants, were analysed and also presented as OR.

5 Results

During the catch-up campaign in 2009, the first dose was given to 194,351 girls (51%), the second dose to 188,897 girls (49%), and the third dose to 174,978 girls (45%). Of the girls who received the first dose, 97% also got the second dose and 93% also the third dose, which means that almost 90% of the girls who started the vaccinations also completed the series.

5.1 Immediate occurring adverse events on locations of mass vaccination

5.1.1 Number of reports

Information was available on 408,662 doses, which is 73% of all administered doses. We received 1107 reports of immediate occurring AEs, resulting in a reporting rate of 27.1 per 10,000 administered doses. For absolute numbers of reports by birth cohort per dose see Figure 1 and for reporting rates by event per dose see Table 1.

Table 1 Incidence rates of reported immediate occurring AEs and medical intervention per 10,000 vaccinated girls

Event	Incidence rate per 10,000 administered doses (95% CI)			
	1st dose	2nd dose	3rd dose	All doses
Presyncope and syncope	20.5 (18.5 – 22.7)	10.4 (8.9 – 12.3)	18.1 (15.3 – 21.5)	16.8 (15.6 – 18.2)
Other vasovagal symptoms	9.9 (8.5 – 11.5)	6.4 (5.2 – 7.8)	5.2 (3.8 – 7.2)	7.9 (7.1 – 8.8)
Jerking	1.39 (0.95 – 2.04)	1.04 (0.63 – 1.71)	1.57 (0.90 – 2.75)	1.32 (1.01 – 1.72)
Vomiting	0.70 (0.41 – 1.19)	0.41 (0.19 – 0.90)	0.53 (0.20 – 1.35)	0.59 (0.40 – 0.87)
Dyspnoea	1.23 (0.82 – 1.85)	0.97 (0.58 - 1.62)	1.97 (1.19 – 3.25)	1.30 (0.99 – 1.70)
Skin symptoms	0.27 (0.11 – 0.62)	0.35 (0.15 – 0.81)	0.53 (0.20 – 1.35)	0.34 (0.20 – 0.58)
Total	**33.8 (31.2 – 36.6)**	**18.3 (16.2 – 20.7)**	**24.0 (20.7 – 27.8)**	**27.1 (25.5 – 28.7)**
Consultation of GP	0.27 (0.10 – 0.66)	0.14 (0.02 – 0.56)	0.26 (0.05 – 1.06)	0.22 (0.11 – 0.43)
Assistance from ambulance staff	0.32 (0.13 – 0.74)	0.21 (0.05 – 0.66)	0.39 (0.10 – 1.25)	0.29 (0.16 – 0.53)

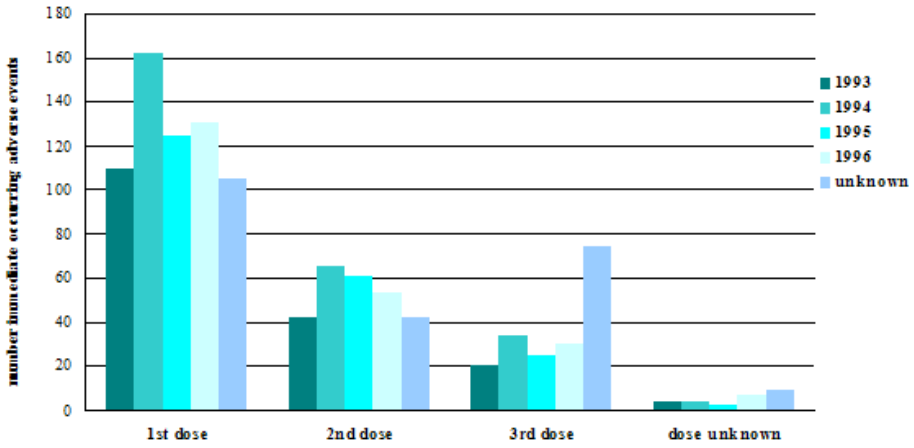

Figure 1 Absolute number of reported immediate occurring AEs by birth cohort and per dose

5.1.2 *Presyncope and syncope*

The most reported immediate occurring AE with 688 reports in total was presyncope and syncope, resulting in a reporting rate of 16.8 per 10,000 administered doses. Jerking and vomiting coincided with presyncope and syncope in 81% (44/54) and 71% (17/24), respectively.

5.1.3 *Other vasovagal symptoms*

Other vasovagal symptoms were reported by 322 girls (reporting rate 7.9 per 10,000 administered doses).

5.1.4 *Rash and itchiness*

Fourteen girls reported rash (reporting rate 0.3 per 10,000 administered doses). Five girls reported itchiness, in all but one case together with rash.

5.1.5 *Dyspnoea*

In 53 cases dyspnoea was reported, only once together with skin problems. In all but two cases, dyspnoea coincided with presyncope and syncope or vasovagal symptoms.

5.1.6 *Anaphylactic shock*

No anaphylactic shock was reported.

5.1.7 *Injury and medical intervention*

An injury was reported 28 times, in all but one case related to presyncope and syncope. Nine girls visited the GP of whom four girls had an injury and 12 girls got assistance from ambulance staff, that was routinely positioned at the locations of mass vaccination (three times because of injury). Table 1 shows the reporting rates of medical interventions per dose.

5.2 Spontaneous reports

5.2.1 Number of reports, reporters, reporting route, and reporting rate

Until 1 January 2010, we received 647 reports of AEFI during the mass vaccination campaign against HPV in 2009. Most reports (n=499; 77.8%) followed after administration of the first dose, 16% (n=106) and 6% (n=39) were reported following the second and third dose, respectively. In three cases the dose number was not known. Most reports were received in the first two months of the campaign. Simultaneously with the start of the administration of second and third dose, the number of reports on the first and second doses increased (Figure 2).

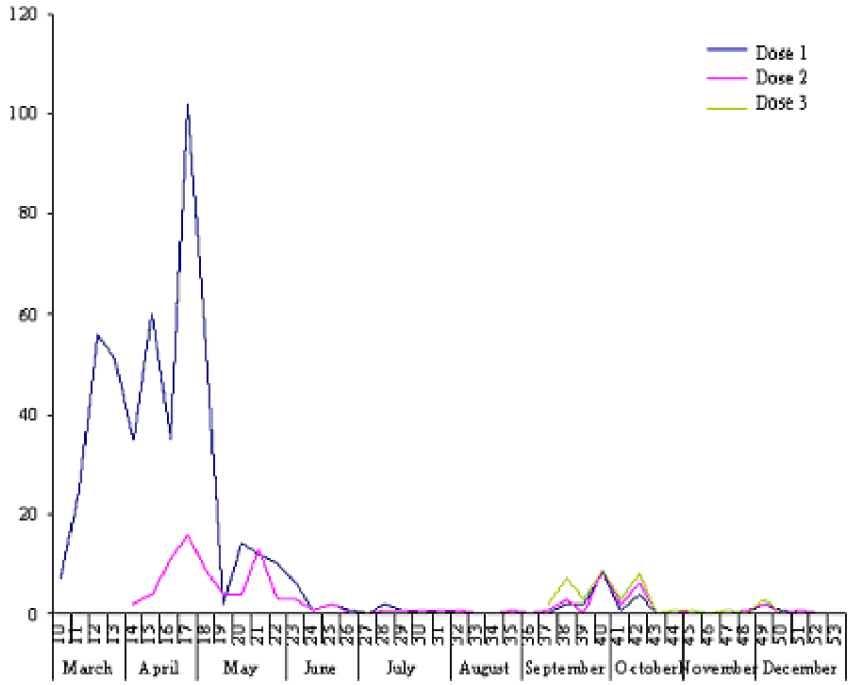

Figure 2 Number of reports by dose per week during the HPV catch-up campaign

One quarter of the reports concerned 13-year-old girls, while in 29%, 29% and 18% of the reports 14-, 15- and 16-year-old girls were involved, respectively.
Professionals of the MHS departments accounted for 72% (n=463) of the reports. Parents were the reporter in 20% (n=127) of the cases. Other reports were sent in by general practitioners (3%), paediatricians (1%), the Netherlands Pharmacovigilance Centre 'Lareb' (1%) and others (2%).
Most reports (66%; n=424) came in by post. Furthermore, 19% (n=123), 10% (n=67), and 4% (n=28) of the notifications were reported by telephone, by e-mail, or digitally, respectively.

Absolute numbers of reports must be seen in relation to the number of vaccinated girls. During the 2009 vaccination campaign 558,226 HPV doses were administered. Therefore, overall reporting rate was 11.6 per 10,000 administered doses (95% CI 10.7-12.5). However, regional reporting rates may differ. Three regions had a lower reporting rate and

one region had a higher reporting rate compared with the nationwide reporting rate (Table 2).

Table 2 Regional distribution of reported AEFI following HPV vaccination per 10,000 administered doses with confidence interval

Region	Reporting rate per 10,000	95% CI*
Groningen	11.1	6.6 - 15.6
Friesland	31.9	24.8 - 39.0
Drenthe	5.6	2.1 - 9.1
Overijssel	14.7	10.2 - 19.3
Flevoland	5.8	1.5 - 10.1
Gelderland	10.1	7.6 - 12.5
Utrecht	12.9	9.4 - 16.4
Noord-Holland	10.1	7.9 - 12.2
Zuid-Holland	13.0	11.0 - 15.1
Zeeland	17.0	10.2 - 23.8
Noord-Brabant	4.4	3.1 - 5.8
Limburg	11.6	8.2 - 15.0
Netherlands	11.6	10.7 - 12.5

*Figures not containing overall reporting rate showed in red.

5.2.2 *Severity of reported events and medical intervention*

The severity of reported AEs is historically categorised in minor and major events (see section 4.2.3). The number of the major events was 87 (13.4%) and for minor events 560 (86.6%).
The level of medical intervention may also illustrate the impact of AEs. In 28.4% (n=184) of the reports no medical help was sought or was not recorded by us. Paracetamol and other home medication was administered in 16.1% (n=104). In 30.6% (n=198) a GP was contacted, resulting in a contact rate of 3.5 per 10,000 administered doses. In 6.6% (n=43) of the reports, girls went to a hospital, giving a consultation rate of 0.8 per 10,000 (Table 3).

Table 3 Intervention and events reported AEFI in the HPV vaccination catch-up campaign (irrespective of causality)

Event	Intervention										
	None	Suppositories[a]	Municipal Health clinic[b]	GP by telephone[c]	GP[d]	Ambulance[e]	Out-patient	Emercency care	Hospital admission	Unknown	Total
Local reaction	22	19	28	5	14	-	1	-	-	16	105
General minor	81	79	57	44	84	-	11	2	1	32	391
illness major	-	-	-	-	1	-	5	1	6	-	13
Skin symptoms	13	2	9	6	33	-	6	-	-	5	74
Faints	12	4	20	3	8	1	3	-	4	1	56
Fits	-	-	-	-	-	2	1	1	-	-	4
Discoloured arms	2	-	1	-	-	-	-	1	-	-	4
Anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-
Encephalopathy/ encephalitis	-	-	-	-	-	-	-	-	-	-	-
Death	-	-	-	-	-	-	-	-	-	-	-
Total	**130**	**104**	**115**	**58**	**140**	**3**	**27**	**5**	**11**	**54**	**647**

[a]paracetamol suppositories, stesolid rectioles and other prescribed or over the counter drugs are included.

[b]telephone call or special visit to the clinic.

[c]consultation of general practitioner by telephone.

[d]examination by general practitioner.

[e]ambulance call and home visit without subsequent transport to hospital.

5.2.3 Causal relation

Events with (likelihood of) causality assessed as certain, probable or possible were considered as adverse reactions (AR) (see section 4.2.4). In this 2009 HPV vaccination campaign, 61.2% (n=394) of reports were adverse reactions, with exclusion of three non-classifiable events. For major events only, 75.6% (n=65) were regarded as AR, while 60.0% (n=329) of the minor AEs was considered to be an AR. There were great differences in causality between the different event categories (Table 4).

Table 4 Causality and events of reported AEFI in HPV vaccination catch-up campaign

Event		Causality				
		Certain Probable Possible	Improbable	Non classifiable	Total	% AR*
Local reaction		105	-	-	105	100
General illness	minor	211	178	2	391	54
	major	-	13	-	13	0
Skin symptoms		23	50	1	74	31
Faints		51	5	-	56	91
Fits		-	4	-	4	0
Discoloured arms		4	-	-	4	100
Anaphylactic shock		-	-	-	-	-
Encephalopathy/ encephalitis		-	-	-	-	-
Death		-	-	-	-	-
Total		**394**	**250**	**3**	**647**	**61**

*Percentage of reports considered adverse reactions (causality certain, probable, possible) excluding non-classifiable events.

5.2.4 *Expert panel*

RIVM very much values a broad scientific discussion on particular or severe reported events. Until 2004, DHC re-evaluated a selection of severe and/or rare events. From 2004 onwards, RIVM has set up an expert panel. Currently this group includes specialists on paediatrics, neurology, immunology, pharmacovigilance, microbiology, vaccinology, and epidemiology. Written assessments are reassessed on diagnosis and causality.
In relation to the HPV catch-up campaign in 2009 the expert panel has focussed on 19 cases (3%). The expert panel agreed in 100% of the reports with (working) diagnosis and causality assessment, determined by RIVM.

5.2.5 *Local reactions*

Local reactions were predominant in 16% (105) of the reports, in 10% (10) concerned as major local reactions because of size, severity, intensity or duration. Inflammation was the most prevalent aspect in 81 reports. Atypical local reactions concerned local rash or discolouration, (de)pigmentation, itching or pain (Table 5).

Table 5 Main (working) diagnosis or symptom in category local reactions of reported AEFI following HPV vaccination catch-up campaign

Symptom or diagnosis	Number of local reactions	AR*
Inflammation	81	81
Atypical reaction	18	18
Haematoma	1	1
Nodule	5	5
Total	**105**	**105**

*Number of considered adverse reactions.

5.2.6 *Minor general illness*

Events that were not classifiable in any of the specific event categories are listed under general illness, depending on severity subdivided in 'minor' or 'major' (see section 4.2.3). In 391 girls the event was considered to be minor illness. Only in a very few times a definite diagnosis was possible; mostly working diagnoses were used (Table 6).

Table 6 Main (working) diagnosis or symptom in category of minor illness of reported AEFI following HPV vaccination catch-up campaign

Symptom or diagnosis	Number of minor illness	AR*
Fever	115	99
Gastro-intestinal tract disorders, including infections	50	23
Menstruation problems	44	0
Headache	44	32
Malaise	38	29
Fatigue	13	5
Airway and lung disorders, including infections	23	3
Rash(illness)	13	0
Dizziness	11	10
Infection	8	0
Other	32	10
Total	**391**	**211**

*Number of considered adverse reactions.

5.2.7 *Major general illness*

Major general illness was recorded 13 times, none of them regarded causally related to the vaccination. Complicated migraine was reported five times; all other events were reported only once. The girl reported with anaphylaxis displayed symptoms three days after the vaccination, shortly after a dinner with shrimps and mussels. Therefore this event was considered not causally related to the vaccination (Table 7).

Table 7 Main (working) diagnosis or symptom in category of major illness of reported AEFI following HPV vaccination catch-up campaign

Symptom or diagnosis	Number of major illness	AR*
Complicated migraine	5	0
Guillain-Barré syndrome	1	0
Bells palsy	1	0
Anaphylaxis	1	0
Severe anaemia	1	0
Viral meningitis	1	0
Severe pain in the back	1	0
Haematuria	1	0
Loss of strength and sensitivity disorder	1	0
Total	**13**	**0**

*Number of considered adverse reactions.

5.2.8 *General skin symptoms*

During the 2009 HPV campaign, skin symptoms were the main or only feature in 74 reports, none of them classified as major. Exanthema/erythema was the most frequent reported event (64%). In 31% a causal relation with the vaccination was assessed (Table 8). Of 65 girls (88%) follow-up information on vaccination status could be traced. In 78% of these girls the next HPV-vaccination was administered, whereby 22% of the girls experienced no adverse event.

Table 8 Main (working) diagnosis or symptom in category general skin symptoms of reported AEFI following HPV vaccination catch-up campaign

Symptom or diagnosis	Number of skin symptoms	AR*
Exanthema/erythema	47	11
Swelling/angio-oedema	6	6
Urticaria	7	2
Itch	4	1
Loss of hair	4	0
Other	6	3
Total	**74**	**23**

*Number of considered adverse reactions.

5.2.9 *Faints*

Through the enhanced passive surveillance system we received 56 reports of presyncope and syncope, of which only five were considered be to a chance occurrence. However, most reports on presyncope and syncope were received through our surveillance of immediate occurring events, which is discussed in section 5.1.

5.2.10 *Fits*

During the 2009 HPV campaign, three convulsions and one atypical attack was reported (see section 4.2.3 for definitions). None of these fits was related to fever. Furthermore, in none of the reports causality with the vaccination was assessed.

5.2.11 *Discoloured arms*

Discolouration of (part of) the arm, in which the vaccination was administered, was reported four times. The eyewitness account from parents or the girl herself showed that these events resemble the discoloured legs syndrome, as described by Kemmeren et al., mainly occurring in infants.[50] A causal relation with the vaccination was assessed in all four reports.

5.3 Survey on tolerability

In total, 5950 e-mail addresses were collected, of which 205 were incorrect. One or more questionnaires were returned by 4248 girls (Table 9). All three questionnaires were returned by 1681 girls.

Table 9 Number of participants of the survey on tolerability by birth cohort

Birth cohort	1st dose (n)	2nd dose[1] (n)	3rd dose[2] (n)	*Complete responders (n)*
1993 (n=1155)	1079	742	561	*456*
1994 (n=1109)	1043	717	559	*457*
1995 (n=1017)	940	637	508	*387*
1996 (n=939)	859	621	490	*377*
Total (n=4248; 73.9%)	**3946 (68.7%)**	**2725 (47.4%)**	**2124 (37.0%)**	***1681 (29.3%)***

[1]Fifteen participants, evenly distributed over birth cohorts, announced to quit receiving the vaccinations after the first dose.
[2]Seven participants, evenly distributed over birth cohorts, announced to quit receiving the vaccinations after the second dose.

5.3.1 Occurrence of adverse events

Table 10 and Figure 3 show the occurrence of AEs within seven days after immunisation after each of the three doses. Of the participating girls, 97.8% reported any AE after the first vaccination, 92.1% reported a local reaction and 91.7% a systemic AE (Table A5.1). A combination of a local reaction and a systemic AE was reported in 85.9% of the girls. After the second and third dose, significantly lower proportions of AEs were reported compared with the first dose (any AE in 90.6% and 92.3%, respectively, local reactions in 79.4% and 83.3%, respectively, and systemic AEs in 78.7% and 78.4%, respectively). The OR for local reactions and for systemic AEs after the second and third dose ranged between 0.32 and 0.43 in comparison with the first vaccination (Table A8.1). Both a local reaction and systemic AEs were reported in 67.4% of the participants after the second dose and in 69.5% after the third dose.

Table 10 Number of reported AEs within seven days after immunisation

Event	1st dose (n=3946) n	2nd dose (n=2725) n	3rd dose (n=2124) n
Local reaction	3633	2163	1770
Systemic AE	3617	2144	1666
Local reaction and systemic AE	*3391*	*1837*	*1476*
Total	**3859**	**2470**	**1960**

A statistically significant age trend in proportions of local reactions and systemic AEs was observed after the first dose. Older girls reported higher proportions than the younger girls. The same age trend was seen for local reactions after the third dose but not after the second dose (Table A5.1). The trend in local reactions is especially caused by the oldest girls (OR 1.45). Girls from the birth cohorts 1993, 1994 and 1995 reported significantly higher proportions of systemic AEs compared with the youngest girls (OR 1.41, OR 1.32, and OR 1.27, respectively) (Table A8.1).

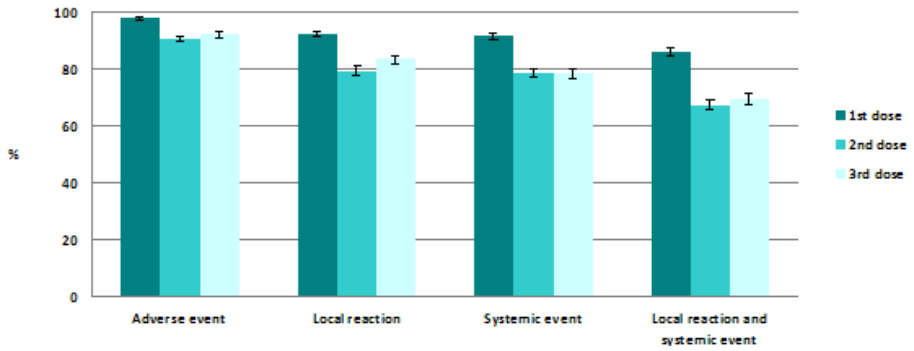

Figure 3 Proportions of reported AEs within seven days after immunisation

The median number of different symptoms per participant was 5 after the first dose and 3 after the second and third dose. The median number of systemic symptoms after the three doses was 3, 1.5, and 2, respectively (range 1 – 21) (Table A5.2).

There were no differences in the proportions of AEs in total between locations of mass vaccination (Table A5.4). Small but statistically significant differences were seen for local reactions and/or systemic AEs after the first dose, in that Amsterdam showed higher proportions compared with the other locations and Geldermalsen showed lower proportions compared with the other locations. Statically significant differences were seen between locations for local reactions after the third dose, especially because of Amsterdam with higher proportions of reported local reactions compared with the other locations.

5.3.2 Local reactions

Figure 4 and Table 11 show the occurrence of local reactions by severity within seven days after immunisation for each of the three doses. Pain at the injection site and reduced use of the arm were the most often reported local reactions (Table A6.1). After the three successive doses 83.7%, 70.9%, and 74.5% of the girls reported pain at the injection site, of which 28.7%, 16.6%, and 19.8% were classified as pronounced, respectively. The older girls (birth cohorts 1993, 1994 and 1995) reported higher proportions of pain at the injection site after the vaccinations compared with the younger girls (birth cohort 1996); OR 1.31, OR 1.26, and OR 1.20, respectively (Table A8.1). Reduced use of the arm was reported in 71.3%, 48.8%, and 52.2% of the girls after the three successive doses. Of these girls 22.1%, 11.4%, and 14.4% reported pronounced reduced use of the arm. Almost all of the local reactions started within 72 hours after immunisation. The median duration increased when the local reaction was more pronounced (between 16.5 and 153.5 hrs) (Table A6.1).

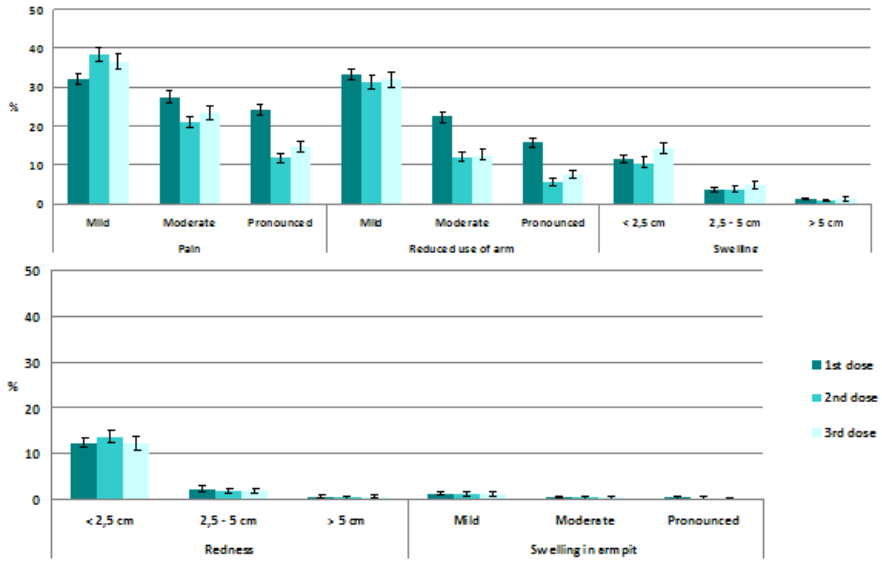

Figure 4 Proportions of reported local reactions within seven days after immunisation

Table 11 Number of reported local reactions within seven days after immunisation

Local reaction	1st dose (n=3946)	2nd dose (n=2725)	3rd dose (n=2124)
	n	n	n
Pain at the injection site	3302	1933	1582
Reduced use of the arm	2815	1330	1108
Swelling	641	415	432
Redness	587	422	302
Swelling in the armpit	76	33	25

5.3.3 *Systemic adverse events*

Table 12 and Figure 5 show the occurrence of systemic AEs within seven days after immunisation for each of the three doses. Myalgia was the most often reported systemic AE, i.e. 75.0%, 55.4%, and 56.5%, respectively (Table A7.1). Also frequent reported systemic AEs were fatigue (33.9%, 22.1%, and 24.1% after the three doses, respectively) and headache (30.0%, 18.1%, and 20.7%, respectively). Fever (≥ 38 °C) was reported in 4.1%, 2.6%, and 4.0% of the girls after the three successive doses. Fainting and vomiting were reported only a very few times (both < 2% after all three doses).

Proportions after the second and third dose were significant lower than after the first dose for almost all systemic AEs (OR, 0.33 – 0.72), only the systemic AEs crying and vomiting were not significantly different between the three successive doses. For cold and cough the proportions after the third dose were higher compared with the first dose (OR 1.14, and OR 1.14, respectively) (Table A8.1).

After the three successive doses 4.5%, 2.1%, and 1.7% of the girls reported other symptoms (Table A7.2). Mostly reported were local

reactions, especially haematoma and lumps on the injection site.
Further, irregular or sudden menstruation was sometimes reported.

Table 12 Number of reported systemic AEs within seven days after immunisation

Systemic AE	**1st dose (n=3946)**	**2nd dose (n=2725)**	**3rd dose (n=2124)**
	n	**n**	**n**
Myalgia	2959	1511	1199
Fatigue	1336	601	512
Headache	1185	492	440
Cold	809	382	486
Dizziness	802	270	209
Listlessness	769	368	250
Abdominal pain	713	290	238
Nausea	643	230	187
Sleeping problems	559	215	168
Joint pain	514	147	101
Muscle contractions	473	142	95
Cough	407	209	248
Itch	400	191	140
Shortness of breath	295	127	112
Rash	243	123	83
Diarrhea	202	94	84
Sweating	194	71	57
Crying	172	102	81
Fever (≥ 38 °C)	160	72	85
Vomiting	62	29	26
Fainting	45	11	13
Other	178	85	66

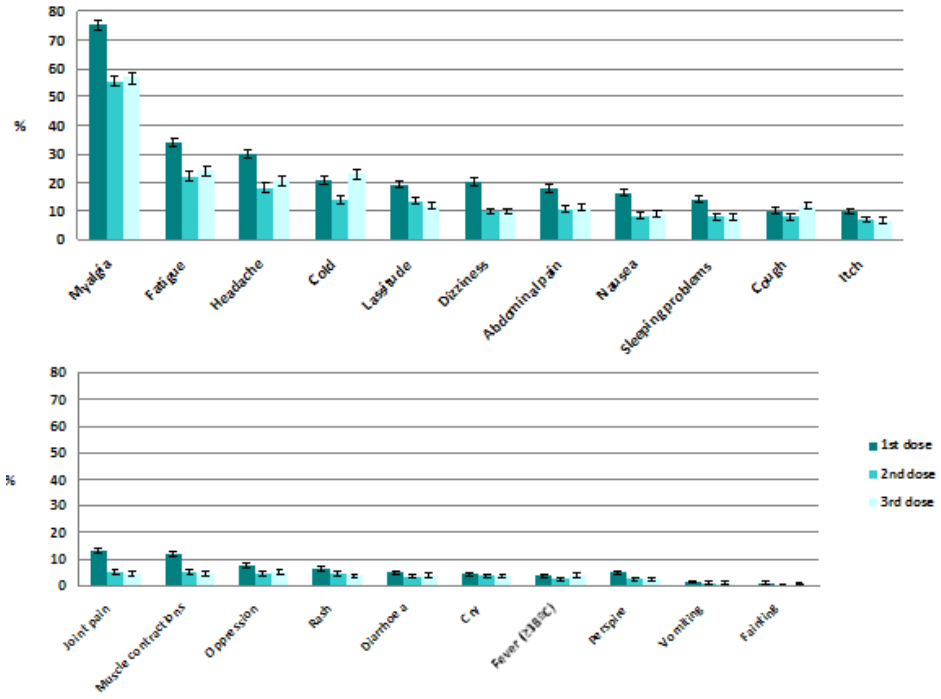

Figure 5 Proportions of reported systemic AEs within seven days after immunisation

5.3.4 *Association between adverse events*

After all three doses, girls with local reactions reported systemic AEs more often (93.3%, 84.9%, and 83.4%, respectively) than girls without local reactions (72.2%, 54.6%, and 53.7%, respectively). This pattern was seen for almost all AEs.
All local reactions were significantly associated with each other with OR ranging from 0.16 to 0.44 for having an AE when another AE was not present compared with when the AE was present (Table A9.1). Some systemic AEs appeared to be strongly associated with each other (OR < 0.1): girls who fainted frequently had fever, fatigue was associated with listlessness and coughing was related to having a cold. Vomiting was associated with fever, nausea and diarrhoea. Girls who were dizzy or experienced shortness of breath were often fainting. Participants who were nauseous experienced frequently also vomiting, dizziness or had abdominal pain (Table A9.3).

5.3.5 *Sickness during the week before or at the time of vaccination and the incidence of underlying illness*

At the time of the first dose 11.7% of the girls had a cold or flu, at the time of the second dose 13.0%, and at the third dose 19.5% (Table A10.1). Girls with a cold or flu at the time of vaccination reported significantly higher proportions of local reactions except for swelling (OR, 1.24-1.70) and systemic AEs except for vomiting, myalgia, muscle contractions and itching (OR, 1.37-6.39) compared with girls without a cold or flu at the time of vaccination (Table A10.4). Of the participants 24.9% had a headache, cold or flu during the week before the first vaccination, in that the older girls reported higher

proportions than younger girls (Table A10.2). Before the second and third dose 21.4% and 29.0% of the girls had a headache, cold, or flu, respectively. Headache (13.6%, 11.3%, and 12.0% for the three vaccinations, respectively) was the sickness reported most often during the week before vaccination. Participants with a headache, cold, or flu during the week before vaccination reported higher proportions of local reactions except for swelling in the armpit (OR, 1.27-1.68) and of systemic AEs except for fainting (OR, 1.27-4.49) compared with girls without a headache, cold or flu during the week before vaccination (Table A10.4).

Underlying illness was present in 33.5% of the participants. Eczema (14.4%) and allergy (12.8%) were the underlying illnesses most often reported (Table A10.3). Girls with underlying illness reported significant higher proportions of the systemic AEs fever, listlessness, cold, cough, shortness of breath, fatigue, sleeping problems, nausea, headache, dizziness, rash and itch than girls without underlying illness, OR 1.16-1.71 (Table A10.4).

5.3.6 Absence and medical interventions

Absence from school, sport, and/or other activities was reported in 15.9%, 7.2%, and 10.4% after the three successive doses, respectively (Table A11.1). Absence from work of the parents or guardians of the vaccinated child was highest after the first dose (2.1% compared with 0.9% and 0.8% after the second and third dose, respectively).

After the first vaccination, 15.0% of the participants used analgesics within seven days after immunisation with a median duration of two days. After the second and third dose fewer analgesics were used, 9.7% and 11.0%, respectively, both with a median duration of one day (Table A11.2). Paracetamol was the most frequently used analgesic.

Other medical interventions were sought by 1.5% of the girls after the first dose, 0.9% after the second dose and 1.1% after the third dose (Table A11.3). Most of them visited a GP (Table 13) or consulted the GP by phone. Girls who sought medical intervention mostly had one or more of the following symptoms: fever, abdominal pain, headache, vomiting, dizziness, fainting and/or rash. Some of the girls contacted the GP only for information about the HPV vaccination.
Two girls visited a specialist after the second dose. In one case causal association of the AE with the vaccination was possible. Four girls visited the emergency room within seven days after vaccination. Follow-up information of the reported symptoms revealed that a causal relation with, either the vaccination was possible in only one case. For the other cases the interval was too long or there were other plausible explanations for the symptoms, or both. None of the girls was admitted to a hospital within seven days after any of the three doses.

Table 13 Number of medical interventions within seven days after immunisation per dose

Intervention	1st dose (n=3946)	2nd dose (n=2725)	3rd dose (n=2124)
	n	n	n
Visited a GP	36	15	14
Consulted GP by phone	25	11	11
Consulted MHS by phone	5	2	1
Visited the emergency room	1	1	2
Visited a medical specialist	0	2	0
Hospitalisation	0	0	0

6 Discussion

6.1 Immediate occurring adverse events on locations of mass vaccination and spontaneous reports of adverse events

6.1.1 Reporting rates

The reporting rate of the combined reports of immediate occurring AEs and the spontaneous reports was 38.7 per 10,000 administered doses. This is higher than in several other countries. For instance in UK vaccination, with the bivalent HPV vaccine implemented in 2008, had a reporting rate of AEFI, received through the Yellow Card Scheme, of 10.5 per 10,000 administered doses.[51]
In the United States of America (USA) the reporting rate in the Vaccine Adverse Event Reporting System (VAERS) was 5.4 per 10,000 administered doses, compared with a rate of 4.1 per 10,000 administered doses in Australia. In both USA and Australia the quadrivalent HPV vaccine was used.[52-53]

The overall reporting rate for the immediate occurring AEs (27.1 per 10,000 doses) following HPV vaccination in the campaign described in this report was comparable with the rate of immediate occurring AEs found during the Meningococcal serotype C (MenC) vaccination campaign in 2002 in the Netherlands (23.3 per 10,000 doses). However, the reporting rate of the enhanced spontaneous reporting system (11.6 per 10,000 doses), routinely in place at RIVM, was much higher for this HPV vaccination campaign than the rate following the mass vaccination campaign against MenC in 2002 in the Netherlands (5.1 per 10,000 doses).[54]

During the MenC vaccination campaign in 2002 there was a positive attitude towards vaccination and vaccination coverage was high. The increased adverse publicity during the HPV vaccination campaign in 2009 concentrated on the safety of the vaccine and therefore may have influenced the number of reported AEFI. Also the age groups and sexes concerned were different in these two campaigns. Furthermore, the MenC vaccination was a single vaccination which also may have influenced the reporting of AEs.

The surveillance of immediate occurring AEs following HPV vaccination did not cover the entire vaccinated population. Therefore, our results could be underestimated because of missing reports. On the other hand, it is more likely that information on mass vaccination sessions where no immediate AEs occurred were not sent to RIVM, resulting in an overestimation.

For both surveillance systems, the reporting rate following the first dose is higher than the rate of the second and third dose. We found no information on dose specific reporting rates in literature. Therefore, we cannot compare our results with other data. Perhaps media attention or specific environmental circumstances at different locations of mass vaccination has played a role. Furthermore, with consecutive doses, professionals routinely ask for AEs after the preceding vaccination

before administering the next dose. This may have influenced the reporting rates per dose, although this phenomenon will have had less influence on the registration of immediate occurring AEs compared with spontaneous AEFI-reports.

6.1.2 Presyncope and syncope

For vaccination with the bivalent HPV vaccine the incidence rate of presyncope and syncope as immediate occurring AE was high (16.8 per 10,000 doses), but comparable with the 2002 mass vaccination campaign against MenC for corresponding age groups. In the MenC campaign the incidence rate of presyncope and syncope was 21.4 per 10,000 doses for 6-to-14-year-old children and 18.9 per 10,000 doses in 15-to-19-year-olds.

In the USA, where the quadrivalent HPV vaccine is used, they estimated a much lower incidence rate of syncope. Based on passive surveillance data the estimated incidence rate was 0.8 per 10,000 vaccinated girls. However, presyncope was not included in this estimation, in contrast to our estimate and they did not have an additional surveillance system for immediate occurring AEs in place.[52]

Buttery et al. described a mass psychogenic response to the quadrivalent HPV vaccine, administered to 12-17-year-old Australian girls. Within several hours after vaccination, girls went to the schools sick bay with symptoms including dizziness, syncope and neurological complaints. Upon further examination no organic basis for the reported symptoms was found.[55] The same type of events was found in Taiwan following vaccination against pandemic influenza A(H1N1).[56]

Perhaps our reports of presyncope and syncope and other vasovagal symptoms also can be categorised as mass psychogenic illness. However, we found a lower reporting rate after the second dose compared with the first and third dose, although the adverse media attention was comparable during the entire 2009-campaign. We found no studies on mass psychogenic illness in which different doses were compared. Clemens stated that immunisation managers should be aware that mass immunisation campaigns could generate such mass reactions and should anticipate on this with improved reporting systems in place capable of distinguishing between multiple cases of conventionally understood vaccine reactions and outbreaks of mass psychogenic illness.[57] The additional surveillance system we used in the Netherlands to monitor immediate occurring events during the mass vaccination campaigns against MenC, against HPV and against pandemic influenza A(H1N1) shows that such a specific surveillance tool works well. However, we received no clustered reports of this kind of events and we cannot fully explain the differences between the doses.

6.1.3 Anaphylaxis

No anaphylactic shock, causally related to the vaccination, was reported. This is not unusual in view of an estimated incidence rate between 1 and 10 per 1,000,000 administered doses in the literature.[39] However, in Australia an incidence rate of anaphylaxis of 0.26 per 10,000 doses was found, whereas in USA the incidence rate of anaphylaxis was estimated at 0.01 per 10,000 doses.[52-53] Some

differences may be the consequence of the use of different case definitions. We did receive one report on anaphylaxis, probably caused by the eating of shrimps and mussels, three days after the vaccination.

6.1.4 Reports of minor adverse events

Minor AEs are divided in 'local reactions' (95/105), 'minor general illness' (all reports) and 'skin symptoms' (all reports).
Regarding local reactions and skin symptoms, no remarkable symptoms were reported. In the category 'minor general illness' the reported AEs are partly causally related to the vaccination. However, adolescent girls frequently complain of symptoms like dizziness, headache and malaise. This must be taken into consideration when assessing causality. This also applies for menstrual problems, mentioned in 11% of the reports in this category. Furthermore, probably the way people experience AEFI is influenced by the symptoms of the disease, the vaccine is targeting. For instance people got a touch of flu after flu-vaccination, headache after a vaccine protecting against meningitis, or cramps and muscle ache after tetanus vaccination. This does not mean people fake AEFI or a causal relation is always absent, but it probably has to do with people's perception and the way to express the unspecific malaise symptoms.

6.1.5 Reports of major adverse events

The number of 'major' AEs was low (n=87). As stated in section 4.2.3, 'major' is not always identical with the definition of SAE. The majority (n=66; 76%) of the major AEs consisted of well known side effects of vaccination, like extended local reactions and fainting, whereby causality with the vaccination was assessed in 61 cases (92%).
Only in 21 cases more rare and severe AEs were reported (see sections 5.2.6, 5.2.9 and 5.2.10). Most of the AEs were only reported once, except complicated migraine (n=5), afebrile convulsions or atypical attacks (n=4) and discoloured legs (n=4). Merely for the reports of discoloured legs causality with the HPV vaccination was assessed as probable.
Migraine is a disorder, frequently becoming manifest during adolescence. Although the standardised causality assessment of each individual report of complicated migraine showed an improbable causal relation in all cases, we will study this possible signal in more detail. Therefore, we currently are assessing the age and sex specific background rates for this disorder. Furthermore, we will study the possibility of association between migraine and HPV vaccination by linking a large electronic general practitioners database with the national vaccination registry 'Praeventis'.
Discoloured leg syndrome is a rare but well known AE in the Netherlands, mainly reported after the first, and sometimes after the second and third dose of dT-IPV-*Haemophilus influenzae* type b (Hib) and pneumococcal conjugate vaccine (PCV7) at two, three and four months of age, administered intramuscularly in the upper thigh. After the MenC vaccination at the age of 14 months in the Netherlands this is seldom reported. It is defined as an even or patchy red, blue or purple discolouration of the leg(s) and/or leg petechiae with or without swelling. The pathophysiology is unknown but may be the result of a vasomotor reaction. Apparently this type of reaction can occur in other limbs and be may triggered by the first contact with a new antigen. Further studies are necessary to gain more insight in this syndrome.[51]

6.2 Survey on tolerability

This study is one of the first population-based studies to assess the frequency of commonly occurring, short-term AEs after mass vaccination with the bivalent HPV-16/18 vaccine. Our study showed that 13-to-16-year-old girls frequently experienced these AEs within seven days after vaccination. Local reactions were reported after each of the three successive doses in 92.1%, 79.4%, and 83.3% of the girls, of those, 22.1%, 12.1%, and 14.8% were classified as pronounced. Systemic AEs were reported after the three successive doses in 91.7%, 78.7%, and 78.4% of the girls, respectively. Pain in the arm and myalgia were the AEs most often reported. This is comparable with results from clinical trials of the bivalent HPV vaccine.[58-63] The frequency of reported AEs was age- and dose- dependent in our study. The proportions AEs were lower after the second and third dose compared with the first dose and were lower for younger girls compared with the older girls. In general, the HPV vaccination was experienced as painful, but the AEs were mostly mild and in all cases transient.

Several clinical trials on the safety and efficacy of the bivalent HPV vaccine showed that pain was the most frequent local reaction, occurring in 60.3% to 93.4% of cases. Although we found comparable proportions of pain, the frequency of pronounced pain was higher in our study (between 11.7% and 24.0%) compared with that in the trials (0.6% - 16.3%).[58-63] In these clinical trials, myalgia was the systemic AE reported most often (16.7% - 52.2%).[58-63] Girls in our study reported higher proportions of myalgia after vaccination (> 55%). An explanation for these differences is unclear, but it may be associated with the difference in the age groups studied; in literature the girls were 10-14-years-old and 15-25-years-old, whereas we studied girls 13-16-years-old. Another possible explanation is the use of different case definitions for AEs, which leads to different definitions of severity. This disparity is why the Brighton Collaboration has addressed the need to develop standardized case definitions for AEs following immunization.[44] The proportions of other frequently reported systemic AEs in our study, such as headache and fatigue, were comparable with that in the trials.[58-63]

The high proportions of local reactions and systemic AEs in this study were comparable to the proportion reported after the diphtheria, tetanus, and inactivated polio vaccination in the Netherlands. This vaccination is given to 9-year-old children and is the last in the NIP before HPV vaccination.[64]

Whereas the literature on HPV vaccination has presented merely the total proportions of AEs after all three doses, we found higher proportions of AEs after the first dose compared with the second and third doses. Several explanations for this dose-dependent reaction are possible. Girls might have been more nervous just before receipt of the first dose, and the resulting tension might have caused more reaction, such as myalgia and pain. However, we have no scientific evidence for this. Another possible explanation is associated with the increased media attention when the vaccination campaign was first begun in 2009. Potentially, this could have led to an increased awareness of AEs,

which may have resulted in an overestimation of reported AEs. The influence of media attention will be evaluated in the future, since we performed the same study during the HPV vaccination campaign in 2010 (a year without increased media attention) among girls 13 to 16 years of age who opted not to participate in 2009 but chose to do so the next year and among 12-year-old girls. Another contributing factor could be that the immune response following the first contact with an antigen varied from that after the second dose. For inactivated vaccines like HPV, in general, several doses are needed to stimulate the production of antibodies and memory cells. The type and concentration of mediators arising after each dose can differ from each other and thereby increase or decrease reactogenicity.[65-69] Whenever a first contact with a live attenuated vaccine results in an adequate immune response, reactogenicity after a booster dose usually is negligible.

An age trend was evident in the reported AEs, in that older girls reported higher proportions than the younger girls. The same trend was also seen for headache in the week before vaccination. When the proportion of AEs reported in clinical trials for 10-14-year-old girls was compared with that of 15-to-25-year-old girls and women, the same effect was seen.[58-62,70-71] An age trend like this was also seen during the first campaign of menC vaccination in the Netherlands in 2002. It is unknown whether this trend in AEs can be explained as an effect of the vaccination. It may have been caused in part by more parents filling in the questionnaire for the younger girls compared with the older girls. Parents may have a different threshold for assessing and reporting AEs than the adolescents who probably report themselves. Unfortunately, we had no information on who completed the questionnaire. Also, in regard to reported headaches, hormonal changes in adolescent girls apparently play a role in such sensitivity.

Because we investigated AEs with a questionnaire-based study, selection bias may have been introduced. We could have overestimated the frequency of AEs when some girls did not return one or more questionnaires because they experienced no AEs in the week after vaccination. We found that the proportions of reported AEs with each dose were similar for all participants and for the girls who returned all three questionnaires. Girls who dropped out of the study showed the same pattern of AEs as the girls who finished the study. So, we have no indication that girls who did not return all three questionnaires comprised a specific subgroup who experienced either more or fewer AEs.

A limitation of the study is that we did not include an unvaccinated control group. Therefore, the frequency of symptoms could not be directly causally linked to the vaccination. The questionnaire contained questions about the occurrence of some symptoms, such as headache, cold, or flu, before the vaccination. After vaccination, the occurrence of these symptoms increased from between 21% and 29% to between 27% and 39%. This shows that the AE reported in our study were just partially related to the vaccination. Girls reported higher proportions of AEs in the presence of underlying illness or sickness before or at the time of vaccination. Analysis of the proportion excluding this group of girls with illness may provide less aberrant results, although it is still uncertain whether all the complaints are causally related to vaccination.

In this study, however, baseline rates of AEs as experienced by girls after vaccination were determined. These data enable us to adequately communicate to the target vaccination group the type of AEs that may be expected after vaccination. The results are also useful for monitoring variations in rates of AEs in the general population or in the target group over time.

7 Conclusions and recommendations

The extended safety surveillance of this HPV campaign in 2009, offered to 13-to-16-year-old girls, gives a good overall view on frequent and rarer solicited and unsolicited AEs after vaccination against HPV. The reporting rate of immediate occurring AEs on mass vaccination locations was high, but comparable to other vaccination campaigns in the Netherlands. The reporting rate of spontaneous reports of AEFI was high, especially after the first dose. However, through both surveillance tools, no rare, severe AEs with a causal relation to the vaccination were reported. In the survey on tolerability, high proportions of local reactions and systemic AEs after vaccination with the bivalent HPV vaccine were reported. Almost all AEs were mild and no serious or unexpected AEs which could be considered related to the vaccination were reported. All these reported commonly occurring AEs were transient.
Therefore we can conclude that the catch-up campaign for girls aged 13 to 16 years (born in 1993 to 1996) with the bivalent HPV vaccine during mass vaccination has been a safe intervention on the short-term. Like with other vaccines we will keep vigilance high for unexpected AEs after vaccination. Up till now we have received no signals for AEs on the longer term.

The study on possible long term AEs is ongoing. At first we have assessed age and sex specific background incidence rates of some immune mediated disorders, which frequently become manifest in adolescence. In the second phase, we will perform data linkage studies to assess possible associations between these disorders and prior HPV vaccination.

Results of this safety surveillance are being used in communication to health care professionals and the public. The results will be presented on the website for professionals and in the information leaflet for girls and their parents. This will contribute to increasing the confidence in HPV vaccination and vaccination in general.

The expected compliance for the catch-up campaign was assessed to be 70% [29], but it turned out to be much lower. The increased media attention before and during the first vaccination sessions could be a possible explanation for this. In addition, there seemed to be a low tendency to include information on this vaccination in school discussions, possibly also due to this adverse media attention. The first vaccination was given to 50% of the invited girls, the second vaccination to 49% and the third to 45% of the girls. Because of this low compliance, girls born in 1993 to 1996 who were not (fully) vaccinated received a new invitation for vaccination against HPV in 2010.[28] Preliminary results of the HPV-campaign in 2010 show a slight increase in vaccine coverage, perhaps due to better communication strategy and decreased adverse publicity.

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List of abbreviations

AE	Adverse event (post-vaccine event)
AEFI	Adverse Event Following Immunisation
AR	Adverse reaction
CI	Confidence interval
CIb	Centre for Infectious Disease Control, the Netherlands
CIN	Cervical intraepithelial neoplasia
DHC	Dutch Health Council
dT-IPV	Diphtheria Tetanus Inactivated Polio (vaccine)
EMA	European Medicines Agency
EPI	Expanded Programme on Immunisation
GLMM	Generalized Linear Mixed Models
GP	General Practitioner
Hib	*Haemophilus influenzae* type b
HPV	Human papillomavirus
ICH	International Conference on Harmonisation
ITP	Idiopathic thrombocytopenic purpura
JGZ	Youth Health Care
LAREB	Netherlands Pharmacovigilance Foundation
MenC	Meningococcal serotype C (vaccine)
MHS	Municipal Health Services
MHS-NL	Municipal Health Services Netherlands
MMR	Measles Mumps Rubella (vaccine)
NIP	National Immunisation Programme
OR	Odds Ratio
PCV	Pneumococcal Conjugate Vaccine
RCP	Regional Coordination Programs
RIVM	National Institute for Public Health and the Environment, the Netherlands
SAE	Serious Adverse Event
SE	Standard Error
SIL	Squamous intraepithelial lesions
VLP	Virus-like particle
WHO	World Health Organisation

Appendix 1 Information leaflet

WAT IS BAARMOEDERHALSKANKER?

Baarmoederhalskanker is een ernstige ziekte. Jaarlijks krijgen ongeveer 600 vrouwen in Nederland deze ziekte. Ongeveer 200 vrouwen overlijden aan baarmoederhalskanker. Zonder behandeling is de ziekte dodelijk.

DE ZIEKTEVERWEKKER

Baarmoederhalskanker krijg je na een infectie met het humaan papillomavirus, kortweg HPV. Veel vrouwen worden in hun leven besmet met dit virus zonder dat ze het merken. Vaak al als tiener of jonge vrouw. Meestal ruimt het lichaam het virus zelf weer op. Bij sommige vrouwen blijft het virus langer zitten en kan er later baarmoederhalskanker ontstaan.

ZO KUN JE HET VIRUS OPLOPEN

Het virus wordt meestal tijdens seks overgebracht. Daarbij is huid op huid contact in de schaamstreek al voldoende. Vanaf de huid kan het virus naar je baarmoeder gaan.

VOORKOM BESMETTING

Door de inenting kun je jezelf beschermen tegen een infectie met het HPV-virus. Je krijgt dan veel minder gemakkelijk baarmoederhalskanker. Inenten heeft het meeste zin bij meisjes die nog geen seks hebben gehad.

VACCINATIE VAN DE OVERHEID

De inenting zit sinds 2009 in het Rijksvaccinatieprogramma, een landelijk programma waar ook andere inentingen in zitten, zoals tegen rodehond en mazelen. De inenting is voor alle meisjes die zijn geboren in 1997 of daarna. Zij krijgen hiervoor een uitnodiging thuis. Ook meisjes die zijn geboren in 1993, 1994, 1995 of 1996 krijgen een uitnodiging.

WIE IN 2009?

Meisjes die in 1993, 1994, 1995 of 1996 geboren zijn, krijgen de inenting in 2009. Ook meisjes die in 1997 vóór 1 september geboren zijn, krijgen de inenting in 2009. Meisjes die na 31 augustus 1997 geboren zijn, krijgen de inenting in de jaren daarna. De inenting is dan steeds op de leeftijd van twaalf jaar.

3 X PRIKKEN

Je krijgt drie prikken om je te beschermen tegen baarmoederhalskanker. De prikken worden in je bovenarm gegeven. Één maand na de eerste prik kun je de tweede prik halen. De derde prik krijg je een half jaar na de eerste prik. Pas na de derde prik ben je beschermd tegen baarmoederhalskanker.

DATUM EN PLAATS

Je krijgt vanzelf een uitnodiging thuis. Daarin staat wanneer je de eerste twee inentingen kunt halen en waar je moet zijn. Zet de afspraken in je agenda en kom op tijd. Je kunt de prik met of zonder je ouders of voogd halen. Voor de derde inenting krijg je een aparte oproep.

BIJWERKINGEN EN WAT ERTEGEN TE DOEN

De meeste meisjes merken niets van de inenting. Sommige meisjes hebben kort na de inenting last van pijn, jeuk, een rode huid of een verdikking op de prikplek. Ook kun je koorts of hoofdpijn krijgen. De meeste klachten zijn mild en gaan vanzelf weer weg.

Bij pijn kun je paracetamol gebruiken, maar meestal is dat niet nodig. Heb je last van de plek waar je bent geprikt? Koel de plek met een nat washandje. Val je gemakkelijk flauw, geef dit dan door aan degene die de prik geeft. Overleg met de huisarts als je na de prik onverwachte klachten krijgt. Die hoeven niet door de prik te komen. Laat het ook weten aan de GGD die de prik heeft gegeven.

GOEDE BESCHERMING

De inenting tegen baarmoederhalskanker geeft een goede bescherming tegen twee veelvoorkomende typen van het HPV-virus. Daarmee kan 70 procent van alle gevallen van baarmoederhalskanker worden voorkomen. Er blijft een kans dat je na vaccinatie later toch baarmoederhalskanker krijgt door een type HPV-virus waar het vaccin niet tegen beschermt. Die kans is wel kleiner dan wanneer je niet ingeënt bent.

ZELF BESLISSEN

Je krijgt ook een prik als je zonder ouder of voogd komt. In de wet is vastgelegd dat bij mensen van twaalf tot en met vijftien jaar een medische handeling kan worden gedaan als zij dat zelf willen. Ook als de ouder(s) of voogd(en) het daar niet mee eens zijn. Neem wel je oproepkaart mee.

INENTINGSGEGEVENS

Als je de prikken haalt, worden jouw inentingsgegevens genoteerd. Die gegevens worden gebruikt om het Rijksvaccinatieprogramma goed uit te voeren en om te onderzoeken of het programma goed werkt.

RIJKSVACCINATIEPROGRAMMA

De inentingen tegen baarmoederhalskanker zijn onderdeel van het Rijksvaccinatieprogramma (RVP). Voor meer informatie over deze vaccinatie kun je kijken op www.prikenbescherm.nl. Meer informatie over het RVP staat op www.rijksvaccinatieprogramma.nl.

Het Rijksinstituut voor Volksgezondheid en Milieu coördineert de communicatie over het Rijksvaccinatieprogramma en werkt daarbij samen met het Nederlands Vaccin Instituut.

rijksvaccinatieprogramma

PRIK EN BESCHERM

VOORKOM BAARMOEDERHALSKANKER

Vanaf 2009 worden meisjes in Nederland gratis ingeënt tegen baarmoederhalskanker.
De inenting is onderdeel van het Rijksvaccinatieprogramma en bestaat uit drie prikken. Meisjes krijgen een persoonlijke uitnodiging voor de inenting.

WWW.PRIKENBESCHERM.NL

Appendix 2 Letter of the Municipal Health Services

BARCODE <linksonder verticaal>

Retouradres: <adres betreffende RCP>

Aan de ouders(s)/verzorgers(s) van

<voornamen> <voorvoegsel> <familienaam>
<Adres> <huisnummer>
<postcode> <woonplaats>
<kixcode>

Geachte ouder(s)/verzorger(s),
Dit is een uitnodiging voor uw dochter om een inenting tegen baarmoederhalskanker te halen. Wilt u deze brief aan haar laten lezen? In de bijgevoegde folder en op de website www.prikenbescherm.nl vindt u meer informatie over de inenting en baarmoederhalskanker.

Hallo,

Binnenkort kun jij je laten inenten tegen baarmoederhalskanker. Alle meisjes geboren op of na 1 januari 1993 tot en met 31 december 1996 ontvangen deze oproep. Baarmoederhalskanker wordt veroorzaakt door een virus. Door de inenting kun je voorkomen dat je besmet raakt met dit virus en heb je later veel minder kans op baarmoederhalskanker. De inenting wordt ook wel HPV-vaccinatie genoemd.

De inenting tegen baarmoederhalskanker wordt drie keer gegeven. De tweede inenting krijg je één maand na de eerste; de derde inenting een half jaar na de eerste. Pas na drie inentingen ben je goed beschermd. Je hoeft niet te betalen; de overheid biedt deze inentingen gratis aan.

Waar je wanneer moet zijn staat in de bijgevoegde brief van de GGD. Je hoeft niet te bellen en kunt gewoon komen. In de envelop zitten ook de oproepkaarten voor de eerste twee inentingen. Die moet je steeds meenemen als je een prik gaat halen. Voor de derde inenting krijg je later een aparte uitnodiging. Neem ook elke keer het HPV-vaccinatiebewijs mee, dan krijg je een stempel als bewijs dat je gevaccineerd bent.

Je kunt samen met één van je ouders de inenting gaan halen, maar je mag ook alleen komen. Je hebt niet per se toestemming van je ouders nodig om geprikt te worden, maar het is wel belangrijk om met je ouders over de inenting te praten.

Heb je nu al één of twee prikken tegen baarmoederhalskanker gehad, dan kun je contact opnemen met RIVM-RCP in jouw regio, telefoonnummer <telefoonnummer betreffende RCP>.

Als je de inenting niet komt halen, bijvoorbeeld omdat je nu al drie prikken tegen baarmoederhalskanker hebt gehad, omdat je zwanger bent of om een andere reden, kun je de antwoordkaart invullen en opsturen. Hierop kun je aangeven waarom je niet komt.

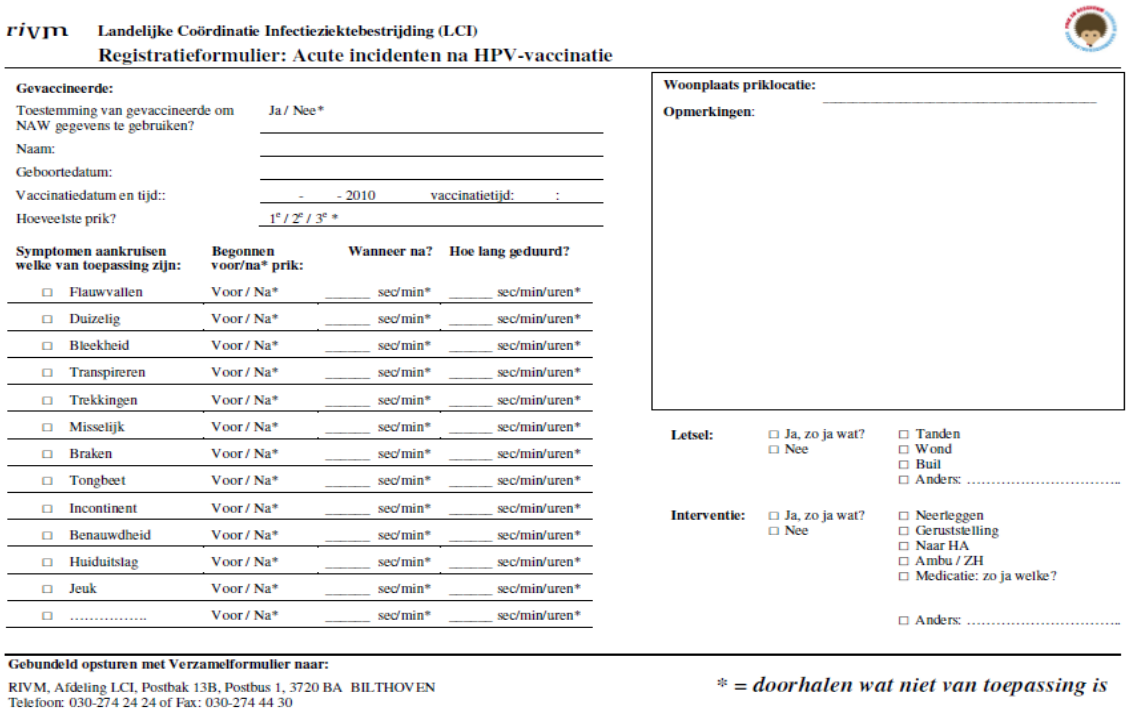
Meer informatie over baarmoederhalskanker en de vaccinatie vind je in de bijgesloten folder of op de website www.prikenbescherm.nl. Mocht je daarna nog vragen hebben, dan kun je bellen met 0800-301 8051.

Met vriendelijke groet,

Prof. dr. R.A. Coutinho
Directeur Centrum Infectieziektebestrijding
Rijksinstituut voor Volksgezondheid en Milieu

Bijlagen:
- brief van de GGD
- 2 oproepkaarten
- antwoordkaart
- vaccinatiebewijs
- folder
- stickers

Appendix 3 Immediate occurring adverse events locations of mass vaccination – Report forms



rivm **Landelijke Coördinatie Infectieziektebestrijding (LCI)**

Registratieformulier: Acute incidenten na HPV-vaccinatie

Gevaccineerde:

Toestemming van gevaccineerde om NAW gegevens te gebruiken? Ja / Nee*

Naam: _____

Geboortedatum: _____

Vaccinatiedatum en tijd:: - - 2010 vaccinatietijd: :

Hoeveelste prik? 1e / 2e / 3e *

Symptomen aankruisen welke van toepassing zijn:	Begonnen voor/na* prik:	Wanneer na?	Hoe lang geduurd?
☐ Flauwvallen	Voor / Na*	_____ sec/min*	_____ sec/min/uren*
☐ Duizelig	Voor / Na*	_____ sec/min*	_____ sec/min/uren*
☐ Bleekheid	Voor / Na*	_____ sec/min*	_____ sec/min/uren*
☐ Transpireren	Voor / Na*	_____ sec/min*	_____ sec/min/uren*
☐ Trekkingen	Voor / Na*	_____ sec/min*	_____ sec/min/uren*
☐ Misselijk	Voor / Na*	_____ sec/min*	_____ sec/min/uren*
☐ Braken	Voor / Na*	_____ sec/min*	_____ sec/min/uren*
☐ Tongbeet	Voor / Na*	_____ sec/min*	_____ sec/min/uren*
☐ Incontinent	Voor / Na*	_____ sec/min*	_____ sec/min/uren*
☐ Benauwdheid	Voor / Na*	_____ sec/min*	_____ sec/min/uren*
☐ Huiduitslag	Voor / Na*	_____ sec/min*	_____ sec/min/uren*
☐ Jeuk	Voor / Na*	_____ sec/min*	_____ sec/min/uren*
☐ ……..	Voor / Na*	_____ sec/min*	_____ sec/min/uren*

Woonplaats priklocatie: _____

Opmerkingen:

Letsel: ☐ Ja, zo ja wat? ☐ Nee
☐ Tanden ☐ Wond ☐ Buil ☐ Anders: ……..

Interventie: ☐ Ja, zo ja wat? ☐ Nee
☐ Neerleggen ☐ Geruststelling ☐ Naar HA ☐ Ambu / ZH ☐ Medicatie: zo ja welke?
☐ Anders: ……..

Gebundeld opsturen met Verzamelformulier naar:

RIVM, Afdeling LCI, Postbak 13B, Postbus 1, 3720 BA BILTHOVEN
Telefoon: 030-274 24 24 of Fax: 030-274 44 30

* = *doorhalen wat niet van toepassing is*

rivm Landelijke Coördinatie Infectieziektebestrijding (LCI)

Verzamelformulier:
Acute incidenten na HPV-vaccinatie

Melder:

Naam: _____

Organisatie: _____

Woonplaats Prik-Locatie: _____

Telefoonnummer: _____

E-mailadres: _____

Vaccinatiedatum: _____

Vaccinatietijd: _____

Partijnummer(s) vaccin: _____

Totaal aantal gegeven vaccinaties deze sessie: _____

Kenmerken Locatie:

- ☐ Sporthal
- ☐ Evenementencomplex
- ☐ Gezondheidscentrum
- ☐ GGD
- ☐ CB
- ☐ Dorpshuis
- ☐ School
- ☐ Anders,

nl: _____

Omstandigheden Locatie:

- ☐ Druk
- ☐ Warm
- ☐ Lang wachten
- ☐ Cluster
- ☐ Anders,

nl: _____

Opmerkingen:

Opsturen met individueel ingevulde formulieren van deze sessie naar:
RIVM, Afdeling LCI, Postbak 13B, Postbus 1, 3720 BA BILTHOVEN
Telefoon: 030-274 24 24 of Fax: 030-274 44 30

Appendix 4 Survey on tolerability – Items questionnaire

- Demographic characteristics:
  - Name
  - Date of birth
  - Postcode
  - Date of completion of the questionnaire
  - Date of vaccination
  - Location of vaccination
  - Time of vaccination (morning/afternoon)
  - Underlying illness (eczema, allergy, asthma, hay fever, diabetes mellitus, other)

- Symptoms during the week before vaccination:
  - Headache
  - Cold
  - Flu
  - Other

- Symptoms at the time of vaccination:
  - Cold
  - Flu
  - Other

- Local reactions within seven days after vaccination (including time interval and duration):
  - Swelling (< 2.5 cm, 2.5 - 5 cm, > 5 cm)
  - Redness (< 2.5 cm, 2.5 - 5 cm, > 5 cm)
  - Pain (mild, moderate, pronounced)
  - Swelling in the armpit (mild, moderate, pronounced)
  - Reduced use of the arm (mild, moderate, pronounced)

- Systemic AEs within seven days after vaccination (including time interval and duration):
  - Fever (continuous)
  - Listlessness
  - Crying
  - Cold
  - Coughing
  - Shortness of breath
  - Fatigue
  - Sleeping problems
  - Nausea
  - Vomiting
  - Diarrhoea
  - Abdominal pain
  - Headache
  - Dizziness
  - Fainting
  - Myalgia
  - Joint pain

Muscle contractions
Sweating
Rash
Itch
Other

- Intervention:
  Use of analgesic (including type and duration)
  Visited a GP
  Consulted a GP by phone
  Consulted MHS by phone
  Visited emergency room
  Visited a medical specialist
  Hospitalisation
  Other

- Absence:
  School
  Sport
  Other activities
  Parents / guardian from work

Appendix 5 Survey on tolerability – Occurrence of adverse events

Table A5.1 Proportions of reported AEs within seven days after immunisation by birth cohort

Birth cohort	1st dose		2nd dose		3rd dose	
	All participants % (95% CI)	Complete responders % (95% CI)	All participants % (95% CI)	Complete responders % (95% CI)	All participants % (95% CI)	Complete responders % (95% CI)
1993	**98.6 (97.7–99.2)**	**98.0 (96.2–99.0)**	**91.5 (89.2–93.4)**	**92.8 (89.9–94.9)**	**94.7 (92.4–96.3)**	**94.3 (91.6–96.2)**
Local reaction	94.1 (92.4–95.4)	94.3 (91.6–96.2)	80.7 (77.7–83.5)	82.7 (78.8–86.0)	87.5 (84.4–90.1)	86.4 (82.8–89.3)
Systemic AE	93.2 (91.5–94.6)	92.8 (89.9–94.9)	79.9 (76.8–82.7)	80.3 (76.2–83.8)	80.4 (76.8–83.5)	78.9 (74.9–82.5)
Local reaction and systemic AE	*88.7 (86.6–90.5)*	*89.0 (85.7–91.7)*	*69.1 (65.7–72.4)*	*70.2 (65.7–74.3)*	*73.3 (69.4–76.8)*	*71.1 (66.6–75.1)*
1994	**97.5 (96.3–98.3)**	**97.2 (95.1–98.4)**	**90.2 (87.8–92.3)**	**89.5 (86.2–92.1)**	**93.0 (90.5–94.9)**	**92.1 (89.2–94.3)**
Local reaction	91.6 (89.7–93.1)	91.0 (87.9–93.4)	79.1 (75.9–82.0)	79.4 (75.4–83.0)	82.8 (79.4–85.8)	81.4 (77.5–84.8)
Systemic AE	93.3 (91.6–94.7)	91.9 (88.9–94.2)	78.7 (75.4–81.6)	77.2 (73.1–81.0)	78.2 (74.5–81.5)	77.2 (73.1–81.0)
Local reaction and systemic AE	*87.3 (85.1–89.3)*	*85.8 (82.2–88.8)*	*67.5 (63.9–70.9)*	*67.2 (62.6–71.4)*	*68.0 (63.9–71.8)*	*66.5 (62.0–70.8)*
1995	**97.2 (95.9–98.1)**	**97.7 (95.5–98.9)**	**91.4 (88.8–93.4)**	**93.3 (90.2–95.5)**	**91.9 (89.1–94.1)**	**91.7 (88.4–94.2)**
Local reaction	90.7 (88.7–92.5)	91.5 (88.1–94.0)	80.2 (76.9–83.2)	80.4 (76.0–84.1)	83.9 (80.3–86.9)	83.7 (79.6–87.2)
Systemic AE	91.5 (89.5–93.2)	91.5 (88.1–94.0)	79.7 (76.4–82.8)	81.1 (76.8–84.8)	78.9 (75.1–82.4)	77.5 (73.0–81.5)
Local reaction and systemic AE	*85.0 (82.5–87.2)*	*85.3 (81.3–88.6)*	*68.6 (64.8–72.2)*	*68.2 (63.3–72.8)*	*70.9 (66.7–74.7)*	*69.5 (64.6–74.0)*
1996	**97.7 (96.4–98.5)**	**97.9 (95.7–99.0)**	**89.2 (86.4–91.5)**	**87.5 (83.7–90.6)**	**89.4 (86.2–91.9)**	**88.1 (84.3–91.1)**
Local reaction	91.4 (89.3–93.1)	89.7 (86.0–92.5)	77.3 (73.8–80.5)	74.8 (70.0–79.0)	79.2 (75.3–82.6)	77.2 (72.6–81.3)
Systemic AE	88.1 (85.7–90.2)	87.5 (83.7–90.6)	76.0 (72.4–79.3)	74.0 (69.2–78.3)	76.1 (72.0–79.8)	73.5 (68.7–77.8)
Local reaction and systemic AE	*81.8 (79.1–84.3)*	*79.3 (74.8–83.2)*	*64.1 (60.2–67.8)*	*61.3 (56.1–66.2)*	*65.9 (61.5–70.1)*	*62.6 (57.5–67.5)*
Total[3]	**97.8 (97.3–98.2)**	**97.7 (96.8–98.3)**	**90.6 (89.5–91.7)**	**90.8 (89.3–92.2)**	**92.3 (91.0–93.4)[1]**	**91.7 (90.2–92.9)[1]**
Local reaction[2]	92.1 (91.2–92.9)[1]	91.7 (90.3–93.0)[1]	79.4 (77.8–80.9)	79.5 (77.5–81.4)[1]	83.3 (81.7–84.9)[1]	82.3 (80.3–84.1)[1]
Systemic AE[2]	91.7 (90.7–92.5)[1]	91.0 (89.5–92.3)[1]	78.7 (77.1–80.2)	78.2 (76.2–80.2)	78.4 (76.6–80.2)	76.9 (74.8–78.9)
Local reaction and systemic AE	*85.9 (84.8–87.0)*	*85.1 (83.3–86.7)*	*67.4 (65.6–69.2)*	*66.9 (64.6–69.2)*	*69.5 (67.5–71.4)*	*67.5 (65.2–69.7)*

For numbers of participants for each dose and by birth cohort see chapter 5 - Table 9.
[1] $p < 0.05$ for trend in comparison of birth cohorts.
[2] $p < 0.05$ for comparison of doses.

Table A5.2 Number of reported AEs within seven days after immunisation per participant

1st dose (n=3946)	Number of AEs					Median number
	0 % (95% CI)	1-4 % (95% CI)	5-9 % (95% CI)	10-14 % (95% CI)	≥15 % (95% CI)	
AEs total	2.2 (1.8–2.7)	42.3 (40.8–43.9)	37.0 (35.5–38.5)	14.9 (13.8–16.0)	3.6 (3.0–4.2)	5
Local reactions	7.9 (7.1–8.8)	91.5 (90.6–92.4)	0.6 (0.4–0.9)	NA	NA	2
Systemic AEs	8.5 (7.6–9.4)	55.1 (53.5–56.6)	27.4 (26.0–28.8)	7.9 (7.1–8.8)	1.2 (0.9–1.6)	3
2nd dose (n=2725)						
AEs total	9.5 (8.4–10.7)	18.9 (17.4–20.4)	26.4 (24.8–28.1)	6.7 (5.8–7.7)	1.8 (1.3–2.4)	3
Local reactions	20.6 (19.1–22.2)	79.0 (77.4–80.5)	0.4 (0.2–0.7)	NA	NA	2
Systemic AEs	21.7 (20.2–23.3)	58.9 (57.1–60.8)	15.4 (14.0–16.8)	3.5 (2.8–4.3)	0.5 (0.3–0.8)	1.5
3rd dose (n=2124)						
AEs total	7.9 (6.8–9.1)	54.4 (56.5–52.2)	28.1 (26.2–30.0)	8.1 (7.0–9.4)	1.6 (1.1–2.2)	3
Local reactions	16.7 (15.1–18.3)	83.1 (81.4–84.7)	0.2 (0.1–0.6)	NA	NA	2
Systemic AEs	21.9 (20.2–23.7)	56.8 (54.6–58.9)	17.3 (15.7–19.0)	3.7 (3.0–4.6)	0.3 (0.1–0.7)	2

NA = not applicable.

Table A5.3 Proportions of reported AEs within seven days after immunisation by location of mass vaccination

Location of vaccination	1st dose			2nd dose			3rd dose		
	Total % (95% CI)	Local reaction[1] % (95% CI)	Systemic AE[1] % (95% CI)	Total % (95% CI)	Local reaction % (95% CI)	Systemic AE % (95% CI)	Total % (95% CI)	Local reaction[1] % (95% CI)	Systemic AE % (95% CI)
Tiel	97.3 (95.5–98.5)	92.6 (89.9–94.6)	92.4 (89.7–94.4)	90.2 (86.7–92.9)	82.3 (78.0–86.0)	79.2 (74.6–83.1)	93.2 (89.3–95.8)	85.3 (80.3–89.2)	74.7 (69.0–79.7)
Geldermalsen	96.0 (93.2–97.7)	89.4 (85.6–92.3)	88.8 (84.9–91.8)	87.0 (82.1–90.7)	76.2 (70.5–81.2)	78.2 (72.6–82.9)	90.1 (85.0–93.7)	78.3 (71.9–83.7)	76.8 (70.3–82.3)
Hilversum	97.4 (96.9–98.4)	91.3 (89.8–92.6)	90.7 (89.2–92.1)	90.1 (88.1–91.9)	78.2 (75.5–80.7)	77.0 (74.3–79.6)	91.0 (88.7–92.8)	81.1 (78.2–83.7)	78.1 (75.0–80.9)
Nieuwegein	98.5 (94.2–99.7)	93.3 (87.4–96.7)	94.1 (88.3–97.2)	90.2 (82.7–94.8)	83.9 (75.5–89.9)	80.4 (71.6–87.0)	94.3 (98.2–85.3)	88.6 (78.2–94.6)	75.7 (63.7–84.8)
Houten	98.1 (96.2–99.1)	91.3 (88.1–93.7)	91.1 (87.5–93.5)	91.5 (87.7–94.2)	77.5 (72.4–81.9)	77.2 (72.1–81.6)	90.8 (86.5–93.8)	78.2 (72.7–82.9)	77.5 (72.0–82.2)
Amsterdam	98.6 (97.5–99.2)	94.4 (92.7–95.8)	94.0 (92.2–95.4)	92.7 (90.2–94.6)	80.5 (77.1–83.5)	81.7 (78.3–84.6)	95.2 (92.7–96.9)	90.4 (87.3–92.8)	82.4 (78.6–85.6)
Other location	95.7 (76.0–99.8)	87.0 (65.3–96.6)	87.0 (65.3–96.6)	95.2 (82.6–99.2)	85.7 (70.8–94.1)	81.0 (65.4–90.9)	94.9 (81.4–99.1)	82.1 (65.9–91.9)	79.5 (63.1–90.1)

[1] $p < 0.05$ for comparison of locations of vaccination.

Appendix 6 Survey on tolerability – Local reactions

Table A6.1 Proportions of reported local reactions within seven days after immunisation by birth cohort

Local reaction	Severity	1st dose				2nd dose				3rd dose			
		All participants		Complete responders		All participants		Complete responders		All participants		Complete responders	
		% (95% CI)[1]	Median duration in hrs	% (95% CI)[1]	Median duration in hrs	% (95% CI)	Median duration in hrs	% (95% CI)[1]	Median duration in hrs	% (95% CI)[1]	Median duration in hrs	% (95% CI)	Median duration in hrs
Pain	**Mild**	32.2 (30.7–33.6)	47.5	32.8 (30.6–35.1)	46.8	38.3 (36.5–40.2)	45.5	38.7 (36.3–41.0)	45.5	36.6 (34.5–38.7)	45.5	38.0 (35.7–40.4)	45.5
	Moderate	27.5 (26.1–28.9)	67.0	29.2 (27.1–31.5)	68.0	20.9 (19.4–22.5)	63.0	21.1 (19.1–23.1)	59.8	23.2 (21.4–25.0)	65.3	22.2 (20.3–24.3)	65.5
	Pronounced	24.0 (22.7–25.4)	84.0	21.1 (19.1–23.1)	77.8	11.7 (10.6–13.0)	81.0	11.4 (9.9–13.0)	76.0	14.7 (13.3–16.3)	83.0	13.1 (11.6–14.9)	80.8
1993	Mild	27.6 (25.0–30.4)	47.0	28.5 (24.5–32.9)	46.5	35.4 (32.0–39.0)	45.8	37.5 (33.1–42.1)	45.0	37.3 (33.3–41.4)	45.0	38.6 (34.1–43.3)	45.5
	Moderate	28.9 (26.2–31.7)	69.0	34.0 (29.7–38.6)	70.0	22.6 (19.7–25.9)	64.0	23.7 (19.9–27.9)	65.0	23.7 (20.3–27.5)	66.0	24.3 (20.5–28.6)	62.0
	Pronounced	28.5 (25.9–31.4)	87.0	23.2 (19.5–27.5)	77.5	13.1 (10.8–15.8)	84.0	11.4 (8.7–14.8)	71.8	17.3 (14.3–20.7)	90.0	15.1 (12.0–18.8)	83.3
1994	Mild	31.2 (28.4–34.1)	50.0	32.4 (28.2–36.9)	46.8	38.2 (34.7–41.9)	46.0	39.4 (34.9–44.0)	46.0	38.1 (34.1–42.3)	44.5	38.1 (33.6–42.7)	45.0
	Moderate	27.9 (25.2–30.7)	66.0	29.5 (25.4–34.0)	66.0	20.6 (17.8–23.8)	60.8	20.8 (17.2–24.9)	57.0	21.3 (18.0–25.0)	68.0	21.0 (17.4–25.1)	68.0
	Pronounced	25.8 (23.2–28.6)	89.5	21.2 (17.6–25.3)	86.0	12.7 (10.4–15.4)	77.5	12.7 (9.8–16.2)	81.0	15.7 (12.9–19.1)	94.0	14.7 (11.6–18.3)	94.8
1995	Mild	34.9 (31.9–38.1)	47.0	34.9 (30.2–39.9)	46.8	37.7 (33.9–41.6)	45.5	36.4 (31.7–41.5)	46.5	35.8 (31.7–40.2)	47.0	39.3 (34.4–44.4)	47.0
	Moderate	26.4 (23.6–29.3)	67.0	27.4 (23.1–32.2)	66.5	22.9 (19.7–26.4)	60.3	23.3 (19.2–27.9)	58.0	24.4 (20.8–28.4)	65.8	21.7 (17.8–26.2)	69.0
	Pronounced	21.9 (19.3–24.7)	82.5	22.0 (18.0–26.5)	76.0	12.2 (9.9–15.1)	75.5	13.2 (10.1–17.1)	71.0	13.8 (11.0–17.2)	79.0	12.4 (9.4–16.2)	76.8
1996	Mild	35.6 (32.4–38.9)	47.3	36.3 (31.5–41.4)	47.3	42.2 (38.3–46.2)	45.0	40.8 (35.9–46.0)	45.3	35.1 (30.9–39.5)	45.0	36.1 (31.3–41.2)	45.0
	Moderate	26.7 (23.8–29.8)	60.0	25.2 (21.0–30.0)	59.3	17.1 (14.2–20.3)	67.0	16.2 (12.7–20.4)	63.5	23.5 (19.8–27.5)	53.5	21.8 (17.8–26.3)	54.0
	Pronounced	18.6 (16.1–21.4)	76.5	17.0 (13.4–21.2)	71.6	8.7 (6.7–11.3)	89.3	8.0 (5.5–11.3)	86.5	11.8 (9.2–15.1)	74.0	9.8 (7.1–13.4)	72.9
Onset within 72 hrs	Mild	31.7 (30.2–33.2)	47.5	32.4 (30.1–34.7)	46.8	37.4 (35.6–39.3)	45.5	38.1 (35.8–40.4)	45.5	36.2 (34.1–38.2)	45.5	37.7 (35.3–40.0)	45.5
	Moderate	27.0 (25.6–28.4)	67.0	29.0 (26.8–31.2)	68.0	20.3 (18.8–21.9)	63.0	20.6 (18.7–22.6)	59.8	22.9 (21.2–24.8)	65.3	22.1 (20.1–24.1)	65.5
	Pronounced	23.6 (22.3–25.0)	84.0	20.7 (18.8–22.7)	77.9	11.6 (10.4–12.8)	81.0	11.3 (9.8–12.9)	76.0	14.5 (13.1–16.1)	83.0	12.9 (11.4–14.6)	80.8

Table A6.1 continuing on the next page

Table A6.1 - Continued

Local reaction	Severity	1st dose				2nd dose				3rd dose			
		All participants		Complete responders		All participants		Complete responders		All participants		Complete responders	
		% (95% CI)[1]	Median duration in hrs	% (95% CI)[1]	Median duration in hrs	% (95% CI)	Median duration in hrs	% (95% CI)[1]	Median duration in hrs	% (95% CI)[1]	Median duration in hrs	% (95% CI)	Median duration in hrs
Reduced use of arm	**Mild**	33.2 (31.8–34.7)	42.0	36.2 (33.9–38.5)	42.0	31.2 (29.4–32.9)	38.0	31.2 (29.0–33.5)	36.0	32.1 (30.1–34.1)	43.0	31.8 (29.6–34.1)	43.0
	Moderate	22.4 (21.1–23.7)	52.0	21.1 (19.2–23.2)	50.0	12.1 (10.9–13.4)	48.0	11.1 (9.6–12.7)	48.0	12.6 (11.2–14.1)	48.0	11.1 (9.7–12.7)	48.0
	Pronounced	15.7 (14.6–16.9)	71.8	13.6 (12.0–15.4)	70.0	5.5 (4.7–6.5)	73.0	5.1 (4.1–6.2)	71.5	7.5 (6.5–8.8)	72.0	6.5 (5.4–7.8)	71.0
1993	Mild	30.2 (27.5–33.1)	39.5	31.1 (27.0–35.6)	40.0	30.5 (27.2–33.9)	40.0	30.3 (26.1–34.7)	33.8	31.0 (27.2–35.1)	41.0	31.1 (27.0–35.6)	41.0
	Moderate	24.3 (21.8–27.0)	50.0	25.2 (21.3–29.5)	48.0	12.5 (10.3–15.2)	47.5	11.8 (9.1–15.3)	46.3	12.5 (9.9–15.6)	48.0	11.4 (8.7–14.8)	48.0
	Pronounced	18.3 (16.0–20.7)	71.0	16.4 (13.2–20.2)	71.0	7.0 (5.3–9.2)	71.9	6.1 (4.2–8.9)	71.6	8.4 (6.3–11.1)	72.0	6.4 (4.4–9.1)	71.5
1994	Mild	32.9 (30.1–35.8)	42.0	38.3 (33.8–42.9)	42.0	29.8 (26.5–33.4)	36.0	31.1 (26.9–35.6)	36.0	31.3 (27.5–35.4)	43.0	31.3 (27.1–35.8)	44.5
	Moderate	21.3 (18.9–23.9)	50.5	19.5 (16.0–23.5)	48.0	12.3 (10.0–15.0)	48.0	9.6 (7.2–12.8)	48.0	12.3 (9.8–15.4)	47.9	10.3 (7.7–13.5)	47.6
	Pronounced	16.7 (14.5–19.1)	76.0	13.3 (10.4–16.9)	70.5	4.7 (3.4–6.6)	71.5	4.8 (3.1–7.3)	71.3	7.5 (5.5–10.1)	71.0	7.2 (5.1–10.1)	71.0
1995	Mild	33.7 (30.7–36.9)	43.5	34.3 (29.7–39.4)	42.0	32.7 (29.0–36.5)	34.3	32.3 (27.7–37.2)	40.5	35.2 (31.1–39.6)	45.0	35.7 (30.9–40.7)	45.0
	Moderate	22.3 (19.7–25.2)	52.5	23.0 (19.0–27.6)	60.0	11.3 (9.0–14.1)	51.5	12.1 (9.1–15.9)	51.7	13.2 (10.4–16.5)	50.3	11.9 (8.9–15.6)	53.3
	Pronounced	14.1 (12.0–16.6)	71.5	13.4 (10.3–17.3)	69.0	6.0 (4.3–8.2)	73.0	6.2 (4.1–9.2)	71.9	8.3 (6.1–11.1)	72.3	7.8 (5.4–11.0)	71.3
1996	Mild	36.8 (33.6–40.1)	43.0	41.4 (36.4–46.5)	43.0	31.9 (28.3–35.7)	41.9	30.8 (26.2–35.7)	39.3	30.8 (26.8–35.1)	39.0	29.2 (24.7–34.1)	39.0
	Moderate	21.4 (18.8–24.3)	53.8	16.4 (12.9–20.7)	52.5	12.4 (10.0–15.3)	51.5	10.9 (8.0–14.6)	53.0	12.4 (9.7–15.8)	47.5	11.1 (8.2–14.9)	47.3
	Pronounced	13.0 (10.9–15.5)	71.0	10.6 (7.8–14.3)	65.5	4.2 (2.8–6.2)	93.0	2.9 (1.5–5.3)	84.0	5.9 (4.1–8.5)	76.5	4.5 (2.7–7.3)	71.0
Onset within 72 hrs	Mild	32.6 (31.1–34.1)	42.0	35.8 (33.5–38.1)	42.0	30.3 (28.6–32.0)	38.0	30.4 (28.2–32.7)	36.0	31.5 (29.5–33.5)	43.0	31.5 (29.3–33.8)	43.0
	Moderate	21.7 (20.4–23.0)	52.0	20.4 (18.5–22.4)	50.0	11.7 (10.5–12.9)	48.0	10.8 (9.4–12.4)	48.0	12.4 (11.0–13.9)	48.0	10.9 (9.5–12.6)	48.0
	Pronounced	15.4 (14.3–16.5)	72.0	13.4 (11.8–15.1)	70.0	5.4 (4.6–6.3)	73.5	5.0 (4.0–6.2)	71.5	7.3 (6.2–8.5)	72.0	6.2 (5.1–7.5)	71.0

Table A6.1 continuing on the next page

Table A6.1 - Continued

Local reaction	Severity	1st dose				2nd dose				3rd dose			
		All participants		Complete responders		All participants		Complete responders		All participants		Complete responders	
		% (95% CI)[1]	Median duration in hrs	% (95% CI)[1]	Median duration in hrs	% (95% CI)	Median duration in hrs	% (95% CI)[1]	Median duration in hrs	% (95% CI)[1]	Median duration in hrs	% (95% CI)	Median duration in hrs
Swelling	**< 2.5 cm**	11.5 (10.5–12.6)	48.0	10.1 (8.7–11.6)	48.0	10.6 (9.6–11.9)	48.0	10.8 (9.4–12.4)	47.0	14.3 (12.8–15.8)	48.0	13.8 (12.2–15.6)	47.6
	2.5–5 cm	3.5 (3.0–4.2)	71.5	3.4 (2.6–4.4)	55.3	3.8 (3.1–4.6)	57.0	3.5 (2.7–4.5)	64.5	4.8 (4.0–5.9)	67.5	4.4 (3.5–5.5)	54.0
	> 5 cm	1.2 (0.9–1.6)	86.5	1.1 (0.7–1.7)	72.0	0.8 (0.5–1.2)	84.0	0.8 (0.4 –1.4)	82.0	1.2 (0.8–1.8)	67.8	1.2 (0.8–1.9)	70.0
1993	< 2.5 cm	13.1 (11.1–15.3)	49.5	12.5 (9.7–16.0)	51.0	12.4 (10.2–15.0)	54.0	14.3 (11.2–17.9)	53.0	17.8 (14.8–21.3)	47.5	17.3 (14.0–21.2)	47.3
	2.5–5 cm	4.4 (3.3–5.8)	84.0	4.8 (3.1–7.3)	90.0	4.2 (2.9–5.9)	68.0	3.9 (2.4–6.3)	64.3	5.2 (3.5–7.4)	54.0	4.8 (3.1–7.3)	54.0
	> 5 cm	2.0 (1.3–3.1)	87.0	1.8 (0.8–3.6)	66.0	0.7 (0.2–1.7)	82.0	0.7 (0.2–2.1)	79.3	2.3 (1.3–4.0)	63.5	2.2 (1.1–4.1)	66.5
1994	< 2.5 cm	12.2 (10.3–14.4)	48.0	10.7 (8.1–14.0)	53.0	11.6 (9.4–14.2)	48.0	11.2 (8.5–14.5)	46.3	14.0 (11.2–17.2)	47.6	13.3 (10.4–16.9)	46.0
	2.5–5 cm	4.1 (3.0–5.6)	78.0	3.1 (1.8–5.2)	63.0	3.8 (2.5–5.5)	65.0	3.7 (2.3–6.0)	67.0	5.7 (4.0–8.1)	72.0	5.0 (3.3–7.6)	72.0
	> 5 cm	1.3 (0.8–2.3)	100.0	1.3 (0.5–3.0)	100.0	0.8 (0.3–1.9)	94.5	0.9 (0.3–2.4)	75.0	0.7 (0.2–2.0)	96.0	0.9 (0.3–2.4)	96.0
1995	< 2.5 cm	9.8 (8.0–11.9)	48.0	6.5 (4.3–9.5)	45.0	8.5 (6.5–11.0)	48.0	8.3 (5.8–11.6)	51.0	12.2 (9.6–15.4)	48.0	11.6 (8.7–15.3)	48.5
	2.5–5 cm	2.4 (1.6–3.7)	49.3	2.8 (1.5–5.2)	45.0	3.1 (2.0–4.9)	45.0	2.1 (1.0–4.2)	45.0	4.3 (2.8–6.6)	54.0	3.6 (2.1–6.1)	54.0
	> 5 cm	0.7 (0.3–1.6)	63.8	0.8 (0.2–2.4)	Unk	1.3 (0.6–2.6)	69.8	1.3 (0.5–3.2)	92.0	1.4 (0.6–2.9)	56.5	1.6 (0.6–3.5)	70.0
1996	< 2.5 cm	10.7 (8.8–13.0)	48.0	10.1 (7.3–13.7)	44.5	10.0 (7.8–12.7)	43.8	9.0 (6.4–12.5)	45.5	12.9 (10.1–16.2)	48.0	12.5 (9.4–16.3)	47.5
	2.5–5 cm	3.1 (2.1–4.6)	66.0	2.4 (1.2–4.6)	61.5	3.9 (2.5–5.8)	46.0	3.7 (2.1–6.3)	42.0	4.1 (2.6–6.3)	58.0	4.0 (2.3–6.6)	53.0
	> 5 cm	0.3 (0.1–1.1)	50.8	0.3 (0.0–1.7)	9.5	0.3 (0.1–1.3)	105.0	0.3 (0.0–1.7)	105.0	0.4 (0.1–1.6)	98.3	0.3 (0.0–1.7)	130.5
Onset within 72 hrs	< 2.5 cm	8.6 (7.7–9.5)	48.0	7.5 (6.3–8.9)	48.0	8.8 (7.8–10.0)	48.0	9.2 (7.9–10.7)	47.0	12.1 (10.7–13.5)	48.0	11.8 (10.3–13.4)	47.5
	2.5–5 cm	2.6 (2.1–3.2)	71.5	2.8 (2.1–3.7)	55.3	3.3 (2.6–4.0)	65.5	3.0 (2.3–4.0)	64.5	4.2 (3.4–5.2)	67.5	3.9 (3.1–5.0)	54.0
	> 5 cm	0.9 (0.6–1.2)	86.5	0.8 (0.4–1.4)	72.0	0.7 (0.4–1.1)	84.0	0.7 (0.4–1.3)	82.0	1.1 (0.7–1.7)	67.8	1.1 (0.7–1.8)	70.0

Table A6.1 continuing on the next page

Table A6.1 – Continued

Local reaction	Severity	1st dose				2nd dose				3rd dose			
		All participants		Complete responders		All participants		Complete responders		All participants		Complete responders	
		% (95% CI)[1]	Median duration in hrs	% (95% CI)[1]	Median duration in hrs	% (95% CI)	Median duration in hrs	% (95% CI)[1]	Median duration in hrs	% (95% CI)[1]	Median duration in hrs	% (95% CI)	Median duration in hrs
Redness	**< 2.5 cm**	12.2 (11.2–13.3)	46.0	11.7 (10.2–13.3)	47.0	13.6 (12.3–14.9)	48.0	13.7 (12.1–15.4)	47.0	12.2 (10.8–13.7)	47.6	12.1 (10.6–13.8)	47.5
	2.5–5 cm	2.2 (1.8–2.8)	76.5	2.0 (1.4–2.8)	65.0	1.7 (1.3–2.3)	60.0	1.2 (0.7–1.9)	63.0	1.6 (1.1–2.3)	72.0	1.4 (0.9–2.1)	67.5
	> 5 cm	0.4 (0.3–0.7)	84.0	0.2 (0.0–0.6)	22.0	0.2 (0.1–0.5)	102.0	0.1 (0.0–0.5)	62.5	0.4 (0.2–0.8)	68.3	0.2 (0.1–0.7)	87.0
1993	< 2.5 cm	11.6 (9.8– 13.7)	46.5	11.4 (8.7–14.8)	47.0	15.1 (12.6–17.9)	51.0	14.9 (11.8–18.6)	49.0	11.4 (9.0–14.4)	47.5	11.2 (8.5–14.5)	47.0
	2.5–5 cm	2.0 (1.3–3.1)	94.3	1.8 (0.8 –3.6)	100.0	2.6 (1.6–4.0)	77.0	2.0 (1.0–3.8)	48.0	2.5 (1.4–4.3)	74.0	1.8 (0.8–3.6)	67.0
	> 5 cm	0.5 (0.2–1.1)	137.0	0.2 (0.0–1.4)	137.0	0.0 (0.0–0.6)	NA	0.0 (0.0–1.0)	NA	0.5 (0.1–1.7)	135.0	0.0 (0.0–1.0)	NA
1994	< 2.5 cm	12.7 (10.7–14.9)	47.5	12.5 (9.7–15.9)	46.5	14.1 (11.7–16.9)	48.0	14.4 (11.4–18.1)	48.0	11.8 (9.3–14.8)	54.0	11.2 (8.5–14.5)	55.5
	2.5 –5 cm	3.0 (2.1–4.2)	72.0	2.6 (1.4–4.7)	54.0	2.0 (1.1–3.3)	55.3	0.9 (0.3–2.4)	74.8	2.0 (1.0–3.6)	72.0	1.8 (0.8–3.6)	70.0
	> 5 cm	0.8 (0.4 –1.6)	90.0	0.2 (0.0–1.4)	21.0	0.1 (0.0–0.9)	117.0	0.0 (0.0–1.0)	NA	0.4 (0.1–1.4)	72.0	0.4 (0.1–1.7)	72.0
1995	< 2.5 cm	12.3 (10.3–14.7)	42.0	11.6 (8.7–15.3)	47.8	12.6 (10.1– 15.4)	45.0	12.4 (9.4–16.2)	44.0	13.8 (11.0–17.2)	47.0	14.2 (11.0–18.2)	44.0
	2.5–5 cm	2.1 (1.3–3.3)	66.0	1.3 (0.5–3.2)	50.0	1.1 (0.5–2.4)	53.5	0.8 (0.2–2.4)	66.0	0.8 (0.3–2.1)	57.9	0.8 (0.2–2.4)	68.0
	> 5 cm	0.0 (0.0–0.5)	NA	0.0 (0.0–1.2)	NA	0.2 (0.0–1.0)	72.0	0.3 (0.0–1.7)	72.0	0.4 (0.1–1.6)	92.0	0.0 (0.0–1.2)	NA
1996	< 2.5 cm	12.0 (9.9–14.4)	47.8	11.1 (8.2–14.9)	45.5	12.4 (10.0–15.3)	46.8	12.7 (9.6– 16.6)	46.8	12.0 (9.4–15.3)	47.3	12.5 (9.4–16.3)	47.5
	2.5–5 cm	1.6 (0.9–2.8)	82.7	1.9 (0.8–4.0)	77.5	1.1 (0.5–2.4)	60.0	1.1 (0.3–2.9)	74.8	1.0 (0.4–2.5)	66.0	1.1 (0.3–2.9)	73.5
	> 5 cm	0.3 (0.1–1.1)	41.5	0.3 (0.0–1.7)	22.0	0.5 (0.1–1.5)	102.0	0.3 (0.0–1.7)	53.0	0.4 (0.1–1.6)	115.5	0.5 (0.1–2.1)	115.5
Onset within 72 hrs	< 2.5 cm	11.7 (10.7–12.7)	46.0	11.2 (9.8–12.9)	47.0	13.0 (11.8–14.4)	47.9	13.1 (11.5–14.8)	46.8	11.9 (10.5–13.3)	47.6	11.8 (10.4–13.5)	47.5
	2.5–5 cm	2.2 (1.8–2.7)	76.5	2.0 (1.4–2.8)	65.0	1.7 (1.3–2.3)	60.0	1.2 (0.7–1.9)	62.3	1.6 (1.1–2.3)	71.5	1.4 (0.9–2.1)	67.5
	> 5 cm	0.4 (0.3–0.7)	84.0	0.2 (0.0–0.6)	22.0	0.2 (0.1–0.5)	102.0	0.1 (0.0–0.5)	62.5	0.4 (0.2–0.8)	100.8	0.2 (0.1–0.7)	87.0

Table A6.1 continuing on the next page

Table A6.1 – Continued

Local reaction	Severity	1st dose				2nd dose				3rd dose			
		All participants		Complete responders		All participants		Complete responders		All participants		Complete responders	
		% (95% CI)[1]	Median duration in hrs	% (95% CI)[1]	Median duration in hrs	% (95% CI)	Median duration in hrs	% (95% CI)[1]	Median duration in hrs	% (95% CI)[1]	Median duration in hrs	% (95% CI)	Median duration in hrs
Swelling in armpit	**Mild**	1.3 (1.0–1.8)	30.0	1.1 (0.7–1.7)	31.3	0.9 (0.6–1.4)	41.0	0.7 (0.4–1.3)	46.0	0.9 (0.6–1.5)	27.0	0.5 (0.3–1.1)	28.5
	Moderate	0.4 (0.2–0.6)	48.0	0.2 (0.0–0.6)	24.0	0.2 (0.1–0.5)	60.0	0.1 (0.0–0.4)	105.0	0.2 (0.1–0.5)	18.0	0.1 (0.0–0.4)	72.0
	Pronounced	0.2 (0.1–0.4)	63.0	0.1 (0.0–0.4)	48.0	0.1 (0.0–0.4)	74.0	0.0 (0.0–0.3)	NA	0.0 (0.0–0.3)	96.0	0.1 (0.0–0.4)	96.0
1993	Mild	1.3 (0.7–2.2)	30.0	0.4 (0.1–1.8)	63.0	1.1 (0.5–2.2)	33.0	0.7 (0.2–2.1)	46.0	1.2 (0.5–2.7)	26.5	0.7 (0.2–2.1)	28.5
	Moderate	0.5 (0.2–1.1)	62.0	0.4 (0.1–1.8)	21.0	0.1 (0.0–0.9)	60.0	0.0 (0.0–1.0)	NA	0.4 (0.1–1.4)	16.5	0.0 (0.0–1.0)	NA
	Pronounced	0.4 (0.1–1.0)	63.0	0.2 (0.0–1.4)	48.0	0.3 (0.0–1.1)	74.0	0.0 (0.0–1.0)	NA	0.0 (0.0–0.8)	NA	0.0 (0.0–1.0)	NA
1994	Mild	1.4 (0.8–2.4)	47.0	1.1 (0.4–2.7)	34.0	0.8 (0.3–1.9)	35.0	0.9 (0.3–2.4)	35.8	1.3 (0.5–2.7)	24.0	0.9 (0.3–2.4)	15.0
	Moderate	0.5 (0.2–1.2)	36.0	0.0 (0.0–1.0)	NA	0.3 (0.0–1.1)	77.8	0.0 (0.0–1.0)	NA	0.0 (0.0–0.9)	NA	0.0 (0.0–1.0)	NA
	Pronounced	0.2 (0.0–0.8)	59.5	0.0 (0.0–1.0)	NA	0.0 (0.0–0.7)	NA	0.0 (0.0–1.0)	NA	0.2 (0.0–1.2)	96.0	0.2 (0.0–1.4)	96.0
1995	Mild	1.9 (1.2–3.1)	28.0	1.8 (0.8–3.9)	24.0	0.6 (0.2–1.7)	39.0	0.8 (0.2–2.4)	39.0	0.6 (0.2–1.9)	54.0	0.0 (0.0–1.2)	NA
	Moderate	0.2 (0.0–0.9)	153.5	0.0 (0.0–1.2)	NA	0.2 (0.0–1.0)	36.0	0.0 (0.0–1.2)	NA	0.0 (0.0–0.9)	NA	0.0 (0.0–1.2)	NA
	Pronounced	0.1 (0.0–0.7)	12.0	0.0 (0.0–1.2)	NA	0.0 (0.0–0.7)	NA	0.0 (0.0–1.2)	NA	0.0 (0.0–0.9)	NA	0.0 (0.0–1.2)	NA
1996	Mild	0.7 (0.3–1.6)	26.3	1.1 (0.3–2.9)	35.3	1.1 (0.5–2.4)	75.0	0.5 (0.1–2.1)	78.0	0.6 (0.2–1.9)	42.0	0.5 (0.1–2.1)	60.0
	Moderate	0.3 (0.1–1.1)	35.0	0.3 (0.0–1.7)	24.0	0.2 (0.0–1.0)	105.0	0.3 (0.0–1.7)	105.0	0.4 (0.1–1.6)	72.0	0.3 (0.0–1.7)	72.0
	Pronounced	0.1 (0.0–0.8)	132.0	0.0 (0.0–1.3)	NA	0.2 (0.0–1.0)	Unk	0.0 (0.0–1.3)	NA	0.0 (0.0–1.0)	NA	0.0 (0.0–1.3)	NA
Onset within 72 hrs	Mild	1.3 (1.0–1.7)	31.0	1.1 (0.7–1.7)	31.3	0.8 (0.5–1.3)	41.0	0.7 (0.4–1.3)	46.0	0.9 (0.6–1.5)	27.0	0.5 (0.3–1.1)	28.5
	Moderate	0.4 (0.2–0.6)	48.0	0.2 (0.0–0.6)	24.0	0.2 (0.1–0.5)	60.0	0.1 (0.0–0.4)	105.0	0.2 (0.1–0.5)	18.0	0.1 (0.0–0.4)	72.0
	Pronounced	0.2 (0.1–0.4)	63.0	0.1 (0.0–0.4)	48.0	0.0 (0.0–0.2)	100.0	0.0 (0.0–0.3)	NA	0.0 (0.0–0.3)	96 0	0.1 (0.0–0.4)	96.0

Unk = unknown, NA = not applicable.
For numbers of participants for each dose and by birth cohort see chapter 5 - Table 9.
[1]$p < 0.05$ for trend in comparison of birth cohorts.

Appendix 7 Survey on tolerability – Systemic adverse events

Table A7.1 Proportions of reported systemic AEs within seven days after immunisation by birth cohort

Systemic AE	1st dose				2nd dose				3rd dose			
	All participants		Complete responders		All participants		Complete responders		All participants		Complete responders	
	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days
Myalgia	75.0 (73.6 – 76.3)[1]	3.0	75.2 (73.0 – 77.2)[1]	3.0	55.4 (53.6 – 57.3)	3.0	55.7 (53.3 – 58.1)	2.0	56.5 (54.3 – 58.6)	3.0	55.9 (53.4 – 58.2)	3.0
1993	76.9 (74.3 – 79.4)	3.0	78.9 (74.9 – 82.5)	3.0	58.2 (54.6 – 61.8)	3.0	58.1 (53.4 – 62.7)	3.0	60.4 (56.2 – 64.5)	3.0	59.0 (54.3 – 63.5)	3.0
1994	76.9 (74.2 – 79.4)	3.0	76.4 (72.1 – 80.1)	3.0	55.9 (52.2 – 59.6)	3.0	53.6 (48.9 – 58.2)	2.0	55.3 (51.0 – 59.4)	3.0	55.8 (51.1 – 60.4)	3.0
1995	76.1 (73.2 – 78.7)	3.0	77.8 (73.2 – 81.8)	3.0	55.3 (51.3 – 59.2)	2.0	58.4 (53.3 – 63.3)	2.0	58.5 (54.0 – 62.8)	3.0	56.6 (51.5 – 61.6)	3.0
1996	69.2 (65.9 – 72.2)	3.0	66.8 (61.8 – 71.5)	3.0	51.5 (47.5 – 55.5)	2.0	52.5 (47.3 – 57.6)	2.0	51.6 (47.1 – 56.1)	2.0	51.7 (46.6 – 56.9)	2.0
Onset within 24 hrs	51.0 (49.4 – 52.5)	3.0	51.7 (49.3 – 54.1)	3.0	38.5 (36.7 – 40.4)	2.0	39.1 (36.8 – 41.5)	2.0	40.4 (38.3 – 42.5)	3.0	39.7 (37.4 – 42.1)	3.0
Fatigue	33.9 (32.4 – 35.4)[1]	3.0	28.7 (26.5 – 30.9)[1]	3.0	22.1 (20.5 – 23.7)	3.0	20.9 (19.0 – 22.9)	3.0	24.1 (22.3 – 26.0)	3.0	21.1 (19.1 – 23.1)	3.0
1993	37.4 (34.6 – 40.4)	3.0	30.9 (26.7 – 35.4)	3.0	22.8 (19.8 – 26.0)	3.0	21.1 (17.5 – 25.1)	3.0	25.8 (22.3 – 29.7)	3.0	23.0 (19.3 – 27.2)	3.0
1994	37.0 (34.1 – 40.0)	3.0	33.9 (29.6 – 38.5)	3.0	23.7 (20.7 – 27.0)	3.0	22.1 (18.4 – 26.2)	3.0	25.6 (22.1 – 29.4)	3.0	23.0 (19.3 – 27.2)	4.0
1995	31.2 (28.2 – 34.3)	3.0	24.3 (20.2 – 28.9)	3.0	22.3 (19.2 – 25.8)	3.0	22.0 (18.0 – 26.5)	3.0	25.8 (22.1 – 29.9)	3.0	22.2 (18.2 – 26.8)	4.0
1996	28.4 (25.4 – 31.6)	3.0	24.1 (20.0 – 28.8)	3.0	19.3 (16.3 – 22.7)	3.0	18.3 (14.6 – 22.7)	3.0	18.8 (15.5 – 22.6)	3.0	15.1 (11.7 – 19.2)	3.0
Onset within 24 hrs	15.5 (14.4 – 16.7)	3.0	12.6 (11.0 – 14.3)	3.0	9.7 (8.6 – 10.8)	2.0	8.3 (7.1 – 9.8)	3.0	10.4 (9.2 – 11.8)	3.0	9.0 (7.7 – 10.5)	3.0
Headache	30.0 (28.6 – 31.5)	2.0	27.2 (25.1 – 29.5)	2.0	18.1 (16.6 – 19.6)	2.0	16.8 (15.0 – 18.7)	2.0	20.7 (19.0 – 22.5)	2.0	18.9 (17.0 – 20.8)	2.0
1993	30.5 (27.8 – 33.4)	2.0	27.0 (23.0 – 31.3)	2.0	19.5 (16.8 – 22.6)	2.0	17.5 (14.2 – 21.4)	2.0	20.3 (17.1 – 23.9)	3.0	17.8 (14.4 – 21.7)	2.0
1994	32.5 (29.7 – 35.5)	2.0	30.6 (26.5 – 35.1)	2.0	19.0 (16.2 – 22.1)	2.0	17.9 (14.6 – 21.8)	2.0	21.5 (18.2 – 25.2)	2.0	20.4 (16.8 – 24.4)	2.0
1995	30.0 (27.1 – 33.1)	2.0	28.7 (24.3 – 33.5)	1.0	18.8 (15.9 – 22.1)	2.0	19.4 (15.6 – 23.7)	2.0	23.2 (19.7 – 27.2)	2.0	23.3 (19.2 – 27.9)	2.0
1996	26.9 (24.0 – 30.0)	2.0	22.3 (18.2 – 26.9)	2.0	14.7 (12.0 – 17.7)	2.0	11.9 (8.9 – 15.7)	2.0	24.1 (20.4 – 28.2)	2.0	13.8 (10.6 – 17.8)	2.0
Onset within 24 hrs	12.6 (11.6 – 13.7)	2.0	10.4 (9.0 – 12.0)	2.0	7.6 (6.6 – 8.6)	2.0	6.4 (5.3 – 7.7)	2.0	7.1 (6.1 – 8.6)	2.0	6.7 (5.6 – 8.1)	2.0
Cold	20.5 (19.3 – 21.8)	5.0	18.6 (16.7 – 20.5)	5.0	14.0 (12.7 – 15.4)	5.0	14.0 (12.4 – 15.8)	5.0	22.9 (21.1 – 24.7)	5.0	20.8 (18.9 – 22.9)	5.0
1993	20.1 (17.8 – 22.7)	5.0	18.9 (15.4 – 22.8)	5.5	13.2 (10.9 – 15.9)	5.0	13.2 (10.3 – 16.7)	5.0	24.6 (21.1 – 28.4)	5.0	21.5 (17.9 – 25.6)	5.0
1994	20.6 (18.2 – 23.2)	5.0	18.4 (15.0 – 22.3)	5.0	16.2 (13.6 – 19.1)	5.0	16.6 (13.4 – 20.4)	5.0	22.0 (18.7 – 25.7)	6.0	21.2 (17.6 – 25.3)	6.0
1995	21.5 (18.9 – 24.3)	5.0	17.8 (14.2 – 22.1)	4.0	16.2 (13.4 – 19.3)	6.0	15.5 (12.1 – 19.6)	5.0	22.2 (18.8 – 26.2)	5.0	19.9 (16.6 – 24.3)	5.0
1996	20.0 (17.4 – 22.9)	5.0	19.4 (15.6 – 23.8)	5.0	10.3 (8.1 – 13.0)	5.0	10.6 (7.8 – 14.3)	5.0	22.7 (19.1 – 26.7)	5.0	20.4 (16.5 – 24.9)	4.0
Onset within 24 hrs	5.5 (4.8 – 6.3)	7.0	4.8 (3.9 – 6.0)	6.0	5.0 (4.2 – 5.9)	7.0	5.2 (4.2 – 6.4)	7.0	7.7 (6.6 – 8.9)	6.0	7.0 (5.9 – 8.4)	6.5

Table A7.1 continuing on the next page

Table A7.1 – Continued

Systemic AE	1st dose				2nd dose				3rd dose			
	All participants		Complete responders		All participants		Complete responders		All participants		Complete responders	
	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days
Listlessness	19.5 (18.3 – 20.8)[1]	2.0	15.8 (14.1 – 17.6)	2.0	13.5 (12.3 – 14.9)	2.0	12.1 (10.6 – 13.8)	2.0	11.8 (10.4 – 13.2)[1]	2.0	9.8 (8.5 – 11.4)[1]	2.0
1993	21.2 (18.8 – 23.8)	2.0	15.8 (12.6 – 19.5)	2.0	11.7 (9.5 – 14.3)	2.0	11.0 (8.3 – 14.3)	2.5	11.6 (9.1 – 14.6)	2.0	10.1 (7.6 – 13.3)	2.0
1994	22.8 (20.3 – 25.5)	2.0	20.4 (16.8 – 24.4)	2.0	15.5 (13.0 – 18.4)	2.0	13.8 (10.8 – 17.4)	2.0	11.8 (9.3 – 14.8)	2.0	10.1 (7.5 – 13.3)	3.0
1995	17.2 (14.9 – 19.8)	2.0	15.2 (11.9 – 19.3)	2.0	13.7 (11.1 – 16.6)	2.0	11.6 (8.7 – 15.3)	2.0	13.4 (10.6 – 16.7)	2.0	11.1 (8.2 – 14.8)	3.0
1996	15.5 (13.2 – 18.1)	2.0	10.6 (7.8 – 14.3)	2.0	13.2 (10.7 – 16.2)	2.0	11.9 (8.9 – 15.7)	2.0	10.2 (7.7 – 13.3)	2.0	7.7 (5.3 – 11.0)	2.0
Onset within 24 hrs	7.6 (6.8 – 8.5)	2.0	5.5 (4.5 – 6.7)	2.0	5.4 (4.6 – 6.3)	2.0	4.6 (3.7 – 5.7)	2.0	4.9 (4.1 – 6.0)	2.0	4.2 (3.3 – 5.3)	2.0
Abdominal pain	18.1 (16.9 – 19.3)	2.0	16.3 (14.6 – 18.2)	1.0	10.6 (9.5 – 11.9)	2.0	9.9 (8.5 – 11.4)	2.0	11.2 (9.9 – 12.6)[1]	2.0	10.1 (8.7 – 11.7)	2.0
1993	16.5 (14.4 – 18.9)	2.0	14.3 (11.2 – 17.9)	2.0	10.1 (8.1 – 12.6)	2.0	9.2 (6.8 – 12.3)	2.0	8.2 (6.1 – 10.9)	2.0	7.9 (5.7 – 10.9)	2.0
1994	19.6 (17.2 – 22.1)	2.0	18.2 (14.8 – 22.1)	1.0	11.3 (9.1 – 13.9)	2.0	10.7 (8.1 – 14.0)	2.0	12.7 (10.1 – 15.8)	2.0	11.8 (9.1 – 15.2)	2.0
1995	19.4 (16.9 – 22.1)	2.0	18.6 (14.9 – 22.9)	1.0	11.5 (9.1 – 14.3)	2.0	11.1 (8.2 – 14.8)	1.0	11.4 (8.8 – 14.6)	2.0	11.4 (8.5 - 15.1)	2.0
1996	16.9 (14.5 – 19.6)	2.0	14.3 (11.0 – 18.4)	1.5	9.7 (7.5 – 12.3)	2.0	8.5 (6.0 – 11.9)	1.0	12.9 (10.1 – 16.2)	2.0	9.5 (6.9 – 13.1)	1.0
Onset within 24 hrs	4.8 (4.2 – 5.5)	2.0	3.7 (2.9 – 4.8)	1.0	2.9 (2.3 – 3.6)	2.0	2.3 (1.6 – 3.1)	1.0	3.1 (2.4 – 3.9)	2.0	2.4 (1.8 – 3.3)	2.0
Sleeping problems	14.2 (13.1 – 15.3)[1]	3.0	10.1 (8.7 – 11.7)[1]	3.0	7.9 (6.9 – 9.0)	3.0	7.1 (5.9 – 8.4)	3.0	7.9 (6.8 – 9.2)	3.0	6.4 (5.3 – 7.7)	3.0
1993	17.2 (15.1 – 19.7)	3.0	12.7 (9.9 – 16.2)	2.5	8.1 (6.3 – 10.3)	3.0	7.0 (4.9 – 9.9)	3.0	8.9 (6.7 – 11.7)	3.5	6.6 (4.6 – 9.4)	3.5
1994	14.1 (12.1 – 16.4)	3.0	10.9 (8.3 – 14.3)	3.0	7.5 (5.8 – 9.8)	3.0	7.0 (4.9 – 9.8)	3.0	7.0 (5.1 – 9.5)	3.0	5.5 (3.6 – 8.1)	3.0
1995	13.4 (11.3 – 15.8)	3.0	8.3 (5.8 – 11.6)	3.0	8.3 (6.3 – 10.8)	3.0	8.0 (5.6 – 11.3)	3.0	7.9 (5.8 – 10.7)	3.0	7.5 (5.2 – 10.7)	3.0
1996	11.1 (9.1 – 13.4)	3.0	8.0 (5.5 – 11.3)	2.0	7.7 (5.8 – 10.2)	4.0	6.4 (4.2 – 9.5)	3.0	8.0 (5.8 – 10.8)	3.0	6.1 (4.0 – 9.1)	3.0
Onset within 24 hrs	9.6 (8.7 – 10.6)	3.0	6.5 (5.4 – 7.8)	3.0	5.1 (4.3 – 6.0)	3.0	4.1 (3.2 – 5.2)	3.0	5.2 (4.3 – 6.2)	3.0	4.2 (3.3 – 5.3)	3.0
Cough	10.3 (9.4 – 11.3)[1]	5.0	8.7 (7.5 – 10.2)	5.0	7.7 (6.7 – 8.7)	5.0	6.8 (5.7 – 8.2)	5.0	11.7 (10.4 – 13.1)	5.0	10.1 (8.7 – 11.6)	5.0
1993	10.6 (8.8 – 12.6)	6.0	8.6 (6.2 – 11.6)	6.0	8.4 (6.5 – 10.6)	5.0	8.1 (5.9 – 11.1)	5.0	12.1 (9.6 – 15.2)	5.0	9.4 (7.0 – 12.6)	5.0
1994	11.2 (9.4 – 13.3)	5.0	10.1 (7.5 – 13.3)	4.0	8.2 (6.4 – 10.5)	4.0	7.2 (5.1 – 10.1)	5.0	12.3 (9.8 – 15.4)	6.0	11.6 (8.9 – 15.0)	6.0
1995	9.7 (7.9 – 11.8)	6.0	11.9 (8.9 – 15.6)	4.0	7.7 (5.8 – 10.1)	6.0	7.0 (4.7 – 10.1)	6.0	10.8 (8.3 – 13.9)	5.0	10.1 (7.3 – 13.6)	4.0
1996	9.7 (7.8 – 11.9)	4.0	7.7 (5.3 – 11.0)	5.0	6.3 (4.6 – 8.6)	4.0	4.8 (2.9 – 7.6)	4.0	11.2 (8.6 – 14.4)	5.0	8.8 (6.2 – 12.2)	5.0
Onset within 24 hrs	2.7 (2.2 – 3.2)	5.0	2.1 (1.5 – 3.0)	4.0	2.5 (2.0 – 3.2)	6.0	2.4 (1.8 – 3.3)	7.0	3.2 (2.6 – 4.1)	6.0	2.9 (2.1 – 3.8)	6.0

Table A7.1 continuing on the next page

Table A7.1 – Continued

Systemic AE	1st dose				2nd dose				3rd dose			
	All participants		Complete responders		All participants		Complete responders		All participants		Complete responders	
	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days
Itch	10.1 (9.2 – 11.1)	2.0	9.2 (7.8 – 10.7)	1.0	7.0 (6.1 – 8.0)	2.0	6.7 (5.5 – 8.0)	2.0	6.6 (5.6 – 7.8)[1]	2.0	5.6 (4.6 – 6.8)	2.0
1993	10.8 (9.0 – 12.8)	2.0	9.4 (7.0 – 12.6)	2.0	6.5 (4.9 – 8.5)	2.0	6.1 (4.2 – 8.9)	2.0	6.4 (4.6 – 8.9)	2.5	5.7 (3.8 – 8.4)	2.0
1994	10.7 (9.0 – 12.8)	2.0	9.0 (6.6 – 12.1)	1.0	7.8 (6.0 – 10.1)	2.0	7.4 (5.3 – 10.3)	1.5	6.3 (4.5 – 8.7)	2.0	4.8 (3.1 – 7.3)	1.5
1995	8.5 (6.8 – 10.5)	2.0	7.2 (4.9 – 10.4)	2.0	7.7 (5.8 – 10.1)	2.0	7.0 (4.7 – 10.1)	2.0	6.7 (4.7 – 9.3)	2.0	6.2 (4.1 – 9.2)	2.0
1996	10.5 (8.5 – 12.8)	2.0	11.1 (8.2 – 14.9)	1.0	6.1 (4.4 – 8.4)	2.0	6.1 (4.0 – 9.1)	2.0	7.1 (5.1 – 9.9)	2.0	5.8 (3.8 – 8.8)	1.0
Onset within 24 hrs	4.1 (3.5 – 4.8)	2.0	3.6 (2.8 – 4.6)	1.0	3.0 (2.4 – 3.7)	1.0	2.6 (1.9 – 3.5)	1.0	2.8 (2.1 – 3.6)	2.0	2.6 (1.9 – 3.5)	2.0
Joint pain	13.0 (12.0 – 14.1)	2.0	10.4 (9.0 – 11.9)	2.0	5.4 (4.6 – 6.3)[1]	2.0	4.2 (3.3 – 5.3)[1]	2.0	4.8 (3.9 – 5.8)	3.0	3.9 (3.1 – 5.0)	3.0
1993	14.3 (12.3 – 16.5)	2.0	11.8 (9.1 – 15.3)	3.0	4.2 (2.9 – 5.9)	3.0	3.1 (1.8 – 5.2)	2.5	3.0 (1.8 – 4.9)	2.0	2.4 (1.3 – 4.4)	2.0
1994	13.8 (11.8 – 16.1)	2.5	10.7 (8.1 – 14.0)	2.0	5.6 (4.1 – 7.6)	2.0	4.6 (2.9 – 7.1)	2.0	5.0 (3.4 – 7.2)	3.0	4.2 (2.6 – 6.5)	3.0
1995	12.1 (10.1 – 14.4)	2.0	10.1 (7.3 – 13.6)	2.0	6.3 (4.6 – 8.5)	2.0	5.2 (3.3 – 8.0)	2.5	5.5 (3.8 – 8.0)	2.5	5.4 (3.5 – 8.3)	3.0
1996	11.1 (9.1 – 13.4)	2.0	8.5 (6.0 – 11.9)	2.0	5.8 (4.1 – 8.0)	2.5	4.0 (2.3 – 6.6)	2.0	5.7 (3.9 – 8.3)	2.0	4.0 (2.3 – 6.6)	2.0
Onset within 24 hrs	6.6 (5.9 – 7.4)	2.0	4.9 (3.9 – 6.0)	2.0	2.5 (1.9 – 3.1)	2.0	2.0 (1.4 – 2.8)	3.0	2.9 (2.2 – 3.7)	2.0	2.4 (1.7 – 3.3)	2.0
Rash	6.2 (5.4 – 7.0)	3.0	5.6 (4.6 – 6.8)	3.0	4.5 (3.8 – 5.4)	3.0	3.8 (3.0 – 4.9)	3.0	3.9 (3.1 – 4.8)	4.0	3.0 (2.3 – 4.0)	3.0
1993	6.4 (5.0 – 8.1)	3.0	6.6 (4.6 – 9.4)	3.0	4.4 (3.1 – 6.3)	5.0	3.5 (2.1 – 5.8)	3.0	6.4 (4.6 – 8.9)	4.0	5.0 (3.3 – 7.6)	3.0
1994	5.8 (4.5 – 7.4)	2.5	5.5 (3.6 – 8.1)	2.0	4.2 (2.9 – 6.0)	2.0	4.2 (2.6 – 6.5)	2.0	3.4 (2.1 – 5.4)	3.0	2.6 (1.4 – 4.7)	3.0
1995	6.5 (5.0 – 8.3)	3.0	5.7 (3.7 – 8.6)	3.0	5.5 (3.9 – 7.6)	3.0	3.6 (2.1 – 6.1)	2.0	3.0 (1.7 – 4.9)	4.0	2.1 (1.0 – 4.2)	4.0
1996	5.8 (4.4 – 7.7)	3.0	4.5 (2.7 – 7.3)	3.0	4.0 (2.7 – 6.0)	4.0	4.0 (2.3 – 6.6)	4.0	2.7 (1.5 – 4.6)	4.0	2.1 (1.0 – 4.3)	3.5
Onset within 24 hrs	1.9 (1.5 – 2.4)	2.0	1.4 (0.9 – 2.2)	2.0	1.3 (0.9 – 1.8)	3.0	1.0 (0.6 – 1.7)	2.0	1.0 (0.7 – 1.6)	3.0	0.7 (0.3 – 1.2)	3.0
Diarrhoea	5.1 (4.5 – 5.9)[1]	2.0	4.1 (3.2 – 5.2)[1]	2.0	3.4 (2.8 – 4.2)	2.0	3.3 (2.5 – 4.3)	2.0	4.0 (3.2 – 4.9)	2.0	3.5 (2.7 – 4.5)	2.0
1993	6.2 (4.9 – 7.9)	2.0	5.9 (4.0 – 8.6)	2.0	3.2 (2.1 – 4.8)	1.0	2.6 (1.4 – 4.7)	1.5	5.0 (3.4 – 7.2)	2.0	4.6 (2.9 – 7.1)	2.0
1994	5.5 (4.2 – 7.1)	2.0	3.9 (2.4 – 6.3)	1.0	4.9 (3.5 – 6.8)	2.0	5.5 (3.6 – 8.1)	2.0	4.7 (3.1 – 6.8)	2.0	4.6 (2.9 – 7.1)	2.0
1995	5.2 (3.9 – 6.9)	2.0	4.1 (2.5 – 6.8)	2.0	2.8 (1.7 – 4.5)	1.0	2.8 (1.5 – 5.2)	1.0	3.1 (1.9 – 5.2)	2.0	2.8 (1.5 – 5.2)	2.0
1996	3.3 (2.2 – 4.7)	2.0	2.1 (1.0 – 4.3)	2.0	2.6 (1.5 – 4.2)	1.5	2.1 (1.0 – 4.3)	1.5	2.9 (1.6 – 4.9)	1.5	1.6 (0.6 – 3.6)	1.0
Onset within 24 hrs	0.8 (0.5 – 1.1)	3.0	0.8 (0.4 – 1.4)	2.0	0.3 (0.1 – 0.6)	2.0	0.2 (0.1 – 0.7)	2.0	0.7 (0.4 – 1.1)	2.5	0.5 (0.2 – 1.0)	2.5

Table A7.1 continuing on the next page

Table A7.1 – Continued

Systemic AE	1st dose				2nd dose				3rd dose			
	All participants		Complete responders		All participants		Complete responders		All participants		Complete responders	
	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days
Crying	4.4 (3.8 – 5.1)	3.0	3.5 (2.7 – 4.5)	3.0	3.7 (3.1 – 4.5)	3.0	3.3 (2.5 – 4.3)	3.0	3.8 (3.1 – 4.7)	3.0	3.3 (2.5 – 4.3)	3.0
1993	4.8 (3.7 – 6.3)	3.0	4.8 (3.1 – 7.3)	2.0	3.6 (2.5 – 5.3)	2.0	3.3 (1.9 – 5.5)	3.0	4.1 (2.7 – 6.2)	2.0	3.7 (2.3 – 6.0)	3.0
1994	5.0 (3.8 – 6.5)	3.0	4.4 (2.8 - 6.8)	4.0	4.7 (3.4 – 6.6)	3.0	4.6 (2.9 – 7.1)	3.0	4.7 (3.1 – 6.8)	3.0	4.4 (2.8 – 6.8)	2.5
1995	4.0 (2.9 – 5.6)	3.0	2.6 (1.3 – 4.9)	2.5	2.8 (1.7 – 4.5)	4.0	2.1 (1.0 – 4.2)	4.0	3.7 (2.3 – 5.9)	4.0	3.1 (1.7 – 5.5)	3.5
1996	3.3 (2.2 – 4.7)	3.0	1.6 (0.6 – 3.6)	2.0	3.7 (2.4 – 5.6)	2.0	2.9 (1.5 – 5.3)	2.0	2.7 (1.5 – 4.6)	3.0	1.6 (0.6 – 3.6)	2.0
Onset within 24 hrs	1.2 (0.9 – 1.6)	2.0	0.7 (0.3 – 1.2)	4.0	0.9 (0.6 – 1.3)	2.5	0.4 (0.2 – 0.9)	3.0	0.7 (0.4 – 1.2)	2.0	0.5 (0.3 – 1.1)	4.0
Dizziness	20.3 (19.1 – 21.6)[1]	15-30 min	17.5 (15.8 – 19.5)	<15 min	9.9 (8.8 – 11.1)	<15 min	8.9 (7.6 – 10.3)	<15 min	9.8 (8.6 – 11.2)	15-30 min	8.3 (7.0 – 9.7)	15-30 min
1993	21.7 (19.3 – 24.3)	15-30 min	18.2 (14.8 – 22.1)	<15 min	9.4 (7.5 – 11.8)	<15 min	9.2 (6.8 – 12.3)	<15 min	8.6 (6.4 – 11.3)	15-30 min	7.5 (5.3 – 10.4)	15-30 min
1994	22.4 (20.0 – 25.1)	15-30 min	21.2 (17.6 – 25.3)	15-30 min	11.0 (8.9 – 13.6)	15-30 min	10.5 (7.9 – 13.8)	<15 min	9.5 (7.2 – 12.3)	15-30 min	8.1 (5.8 – 11.1)	15-30 min
1995	20.1 (17.6 – 22.8)	15-30 min	17.6 (14.0 – 21.8)	<15 min	10.5 (8.3 – 13.2)	<15 min	10.3 (7.6 – 13.9)	<15 min	11.0 (8.5 – 14.2)	<15 min	10.6 (7.8 – 14.2)	<15 min
1996	17.1 (14.7 – 19.8)	15-30 min	12.5 (9.4 – 16.3)	<15 min	8.7 (6.7 – 11.3)	<15 min	5.0 (3.1 – 7.9)	<15 min	10.4 (7.9 – 13.5)	15-30 min	6.9 (4.6 – 10.1)	15-30 min
Onset within 24 hrs	10.4 (9.5 – 11.4)	15-30 min	8.4 (7.2 – 9.9)	15-30 min	4.3 (3.6 – 5.1)	15-30 min	3.8 (3.0 – 4.9)	15-30 min	3.5 (2.8 – 4.4)	15-30 min	2.7 (2.0 – 3.6)	15-30 min
Nausea	16.3 (15.2 – 17.5)[1]	15-30 min	13.6 (12.0 – 15.4)	15-30 min	8.4 (7.4 – 9.6)	15-30 min	7.9 (6.7 – 9.3)	15-30 min	8.8 (7.7 – 10.1)	>30 min	8.4 (7.1 – 9.8)	15-30 min
1993	16.6 (14.4 – 19.0)	15-30 min	13.6 (10.7 – 17.2)	15-30 min	9.4 (7.5 – 11.8)	15-30 min	8.8 (6.4 – 11.8)	15-30 min	8.2 (6.1 – 10.9)	>30 min	7.7 (5.5 – 10.6)	>30 min
1994	19.0 (16.7 – 21.5)	15-30 min	16.0 (12.8 – 19.7)	15-30 min	8.4 (6.5 – 10.7)	15-30 min	8.1 (5.8 – 11.1)	15-30 min	9.1 (6.9 – 11.9)	>30 min	8.8 (6.4 – 11.8)	>30 min
1995	16.1 (13.8 – 18.6)	>30 min	15.0 (11.7 – 19.0)	>30 min	8.0 (6.1 – 10.5)	15-30 min	8.3 (5.8 – 11.6)	>30 min	8.9 (6.6 – 11.8)	15-30 min	9.3 (6.7 – 12.8)	15-30 min
1996	13.3 (11.1 – 15.8)	15-30 min	9.5 (6.9 – 13.1)	>30 min	7.9 (5.9 – 10.4)	15-30 min	9.0 (6.4 – 12.5)	15-30 min	9.2 (6.8 – 12.2)	>30 min	8.0 (5.5 – 11.3)	>30 min
Onset within 24 hrs	8.0 (7.2 – 8.9)	15-30 min	6.7 (5.5 – 8.0)	15-30 min	3.8 (3.1 – 4.6)	15-30 min	3.5 (2.7 – 4.5)	15-30 min	3.2 (2.5 – 4.1)	>30 min	3.0 (2.3 – 4.0)	>30 min

Table A7.1 continuing on the next page

Table A7.1 – Continued

Systemic AE	1st dose				2nd dose				3rd dose			
	All participants		Complete responders		All participants		Complete responders		All participants		Complete responders	
	% (95% CI)	Median duration	% (95% CI)	Median duration	% (95% CI)	Median duration	% (95% CI)	Median duration	% (95% CI)	Median duration	% (95% CI)	Median duration
Muscle contractions	12.0 (11.0 – 13.1)	<15 min	9.5 (8.1 – 11.0)	<15 min	5.2 (4.4 – 6.1)	<15 min	4.3 (3.4 – 5.4)	<15 min	4.5 (3.7 – 5.5)	<15 min	3.7 (2.9 – 4.8)	<15 min
1993	12.2 (10.4 – 14.4)	<15 min	9.4 (7.0 – 12.6)	<15 min	5.4 (3.9 – 7.3)	<15 min	4.6 (2.9 – 7.1)	<15 min	4.1 (2.7 – 6.2)	<15 min	3.3 (1.9 – 5.5)	<15 min
1994	13.4 (11.4 – 15.7)	<15 min	10.9 (8.3 – 14.3)	<15 min	4.9 (3.5 – 6.8)	<15 min	5.0 (3.3 – 7.6)	<15 min	4.3 (2.8 – 6.4)	<15 min	3.7 (2.3 – 6.0)	15-30 min
1995	11.0 (9.1 – 13.2)	<15 min	8.3 (5.8 – 11.6)	<15 min	6.3 (4.6 – 8.5)	<15 min	5.2 (3.3 – 8.0)	<15 min	5.5 (3.8 – 8.0)	<15 min	5.2 (3.3 – 8.0)	<15 min
1996	11.1 (9.1 – 13.4)	<15 min	9.0 (6.4 – 12.5)	<15 min	4.3 (2.9 – 6.3)	<15 min	2.1 (1.0 – 4.3)	<15 min	4.1 (2.6 – 6.3)	<15 min	2.9 (1.5 – 5.3)	<15 min
Onset within 24 hrs	6.8 (6.0 – 7.6)	<15 min	5.8 (4.8 – 7.1)	<15 min	2.6 (2.1 – 3.3)	<15 min	2.4 (1.8 – 3.3)	<15 min	1.7 (1.2 – 2.4)	<15 min	1.4 (0.9 – 2.2)	<15 min
Shortness of breath	7.5 (6.7 – 8.4)[1]	<15 min	4.9 (4.0 – 6.1)[1]	<15 min	4.7 (3.9 – 5.5)	15-30 min	3.7 (2.9 – 4.7)	15-30 min	5.3 (4.4 – 6.3)	15-30 min	4.6 (3.7 – 5.7)	15-30 min
1993	9.5 (7.9 – 11.5)	<15 min	6.8 (4.7 – 9.6)	<15 min	5.3 (3.8 – 7.2)	15-30 min	3.5 (2.1 – 5.8)	15-30 min	7.1 (5.2 – 9.7)	<15 min	5.7 (3.8 – 8.4)	<15 min
1994	7.5 (6.0 – 9.3)	<15 min	5.0 (3.3 – 7.6)	<15 min	4.3 (3.0 – 6.2)	15-30 min	3.7 (2.3 – 6.0)	15-30 min	4.3 (2.8 – 6.4)	15-30 min	4.4 (2.8 – 6.8)	15-30 min
1995	7.0 (5.5 – 8.9)	15-30 min	4.9 (3.1 – 7.7)	<15 min	4.7 (3.3 – 6.7)	15-30 min	4.4 (2.7 – 7.1)	<15 min	4.5 (3.0 – 6.8)	15-30 min	4.1 (2.5 – 6.8)	15-30 min
1996	5.2 (3.9 – 7.0)	15-30 min	2.7 (1.4 – 5.0)	<15 min	4.3 (2.9 – 6.3)	15-30 min	3.2 (1.7 – 5.6)	15-30 min	4.9 (3.2 – 7.3)	<15 min	3.7 (2.1 – 6.3)	<15 min
Onset within 24 hrs	2.7 (2.2 – 3.2)	15-30 min	1.5 (1.0 – 2.2)	<15 min	1.8 (1.4 – 2.4)	15-30 min	1.5 (1.0 – 2.3)	15-30 min	1.7 (1.2 – 2.4)	15-30 min	1.2 (0.7 – 1.9)	15-30 min
Sweating	4.9 (4.3 – 5.6)	15-30 min	3.6 (2.8 – 4.6)	15-30 min	2.6 (2.1 – 3.3)	15-30 min	2.3 (1.7 – 3.2)[1]	15-30 min	2.7 (2.1 – 3.5)	15-30 min	2.3 (1.7 – 3.2)	15-30 min
1993	4.7 (3.6 – 6.2)	15-30 min	3.5 (2.1 – 5.8)	>30 min	3.0 (1.9 – 4.5)	15-30 min	1.3 (0.5 – 3.0)	15-30 min	3.0 (1.8 – 4.9)	15-30 min	2.4 (1.3 – 4.4)	15-30 min
1994	6.3 (5.0 – 8.0)	15-30 min	4.6 (2.9 – 7.1)	15-30 min	2.1 (1.2 – 3.5)	15-30 min	2.2 (1.1 – 4.1)	15-30 min	2.5 (1.4 – 4.3)	15-30 min	2.4 (1.3 – 4.4)	15-30 min
1995	4.5 (3.3 – 6.0)	15-30 min	3.4 (1.9 – 5.8)	15-30 min	3.3 (2.1 – 5.1)	15-30 min	3.6 (2.1 – 6.1)	15-30 min	3.3 (2.0 – 5.4)	15-30 min	2.8 (1.5 – 5.2)	15-30 min
1996	3.6 (2.5 – 5.1)	15-30 min	2.7 (1.4 – 5.0)	15-30 min	2.1 (1.2 – 3.6)	15-30 min	2.4 (1.2 – 4.6)	<15 min	1.8 (0.9 – 3.6)	15-30 min	1.6 (0.6 – 3.6)	15-30 min
Onset within 24 hrs	1.4 (1.0 – 1.8)	15-30 min	1.0 (0.6 – 1.6)	15-30 min	0.8 (0.5 – 1.3)	<15 min	0.8 (0.4 – 1.4)	<15 min	1.0 (0.6 – 1.5)	15-30 min	0.9 (0.5 – 1.5)	15-30 min
Vomiting	1.6 (1.2 – 2.0)	<15 min	1.4 (0.9 – 2.1)	<15 min	1.1 (0.7 – 1.5)	<15 min	0.8 (0.4 – 1.4)	<15 min	1.2 (0.8 – 1.8)	<15 min	1.0 (0.6 – 1.6)	<15 min
1993	1.7 (1.0 – 2.7)	<15 min	1.5 (0.7 – 3.3)	<15 min	1.2 (0.6 – 2.4)	<15 min	0.9 (0.3 – 2.4)	<15 min	1.6 (0.8 – 3.1)	<15 min	1.1 (0.4 – 2.7)	<15 min
1994	1.6 (1.0 – 2.7)	<15 min	0.9 (0.3 – 2.4)	15-30 min	0.7 (0.3 – 1.7)	<15 min	0.2 (0.0 – 1.4)	15-30 min	1.1 (0.4 – 2.4)	15-30 min	1.1 (0.4 – 2.7)	<15 min
1995	2.1 (1.3 – 3.3)	15-30 min	2.3 (1.1 – 4.5)	15-30 min	1.4 (0.7 – 2.8)	<15 min	1.3 (0.5 – 3.2)	<15 min	1.4 (0.6 – 2.9)	<15 min	0.8 (0.2 – 2.4)	15-30 min
1996	0.8 (0.4 – 1.7)	<15 min	0.8 (0.2 – 2.5)	>30 min	1.0 (0.4 – 2.2)	<15 min	0.8 (0.2 – 2.5)	<15 min	0.8 (0.3 – 2.2)	<15 min	0.8 (0.2 – 2.5)	<15 min
Onset within 24 hrs	0.3 (0.2 – 0.6)	<15 min	0.3 (0.1 – 0.7)	>30 min	0.1 (0.0 – 0.4)	<15 min	0.2 (0.0 – 0.6)	<15 min	0.2 (0.1 – 0.6)	15-30 min	0.1 (0.0 – 0.5)	15-30 min
Fainting	1.1 (0.8 – 1.5)	<15 min	1.1 (0.7 – 1.7)	<15 min	0.4 (0.2 – 0.7)	<15 min	0.4 (0.2 – 0.9)	<15 min	0.6 (0.3 – 1.1)	<15 min	0.3 (0.1 – 0.7)	<15 min
1993	1.9 (1.2 – 3.0)	<15 min	1.3 (0.5 – 3.0)	<15 min	0.3 (0.0 – 1.1)	<15 min	0.0 (0.0 – 1.0)	NA	0.7 (0.2 – 1.9)	<15 min	0.4 (0.1 – 1.8)	<15 min
1994	1.2 (0.6 – 2.1)	<15 min	1.5 (0.7 – 3.3)	<15 min	0.7 (0.3 – 1.7)	<15 min	0.7 (0.2 – 2.1)	<15 min	0.9 (0.3 – 2.2)	<15 min	0.2 (0.0 – 1.4)	<15 min
1995	0.4 (0.1 – 1.2)	<15 min	0.3 (0.0 – 1.7)	<15 min	0.5 (0.1 – 1.5)	<15 min	0.8 (0.2 – 2.4)	<15 min	0.4 (0.1 – 1.6)	<15 min	0.0 (0.0 - 1.2)	NA
1996	0.9 (0.4 – 1.9)	<15 min	1.1 (0.3 – 2.9)	<15 min	0.2 (0.0 – 1.0)	<15 min	0.3 (0.0 – 1.7)	<15 min	0.4 (0.1 – 1.6)	<15 min	0.5 (0.1 – 2.1)	<15 min
Onset within 24 hrs	0.6 (0.4 – 0.9)	<15 min	0.6 (0.3 – 1.1)	<15 min	0.2 (0.1 – 0.5)	<15 min	0.3 (0.1 – 0.7)	<15 min	0.2 (0.1 – 0.6)	<15 min	0.2 (0.0 – 0.6)	<15 min

Table A7.1 continuing on the next page

Table A7.1 – Continued

Systemic AE	1st dose				2nd dose				3rd dose			
	All participants		Complete responders		All participants		Complete responders		All participants		Complete responders	
	% (95% CI)	Median duration in hrs	% (95% CI)	Median duration in hrs	% (95% CI)	Median duration in hrs	% (95% CI)	Median duration in hrs	% (95% CI)	Median duration in hrs	% (95% CI)	Median duration in hrs
Fever (≥ 38 °C)	4.1 (3.5 – 4.7)	36.0	2.9 (2.2 – 3.9)	32.5	2.6 (2.1 – 3.3)[1]	37.0	2.3 (1.7 – 3.2)	36.0	4.0 (3.2 – 4.9)	36.0	3.4 (2.6 – 4.4)	34.5
1993	4.9 (3.7 – 6.4)	33.1	3.5 (2.1 – 5.8)	42.0	1.9 (1.1 – 3.2)	24.0	1.8 (0.8 – 3.6)	26.5	3.4 (2.1 – 5.3)	33.0	2.4 (1.3 – 4.4)	33.0
1994	3.9 (2.9 – 5.3)	42.0	3.5 (2.1 – 5.7)	39.0	2.1 (1.2 – 3.5)	42.0	1.5 (0.7 – 3.3)	45.0	3.9 (2.5 – 6.0)	36.0	3.3 (1.9 – 5.5)	42.0
1995	3.9 (2.8 – 5.4)	36.0	2.6 (1.3 – 4.9)	35.5	3.1 (2.0 – 4.9)	32.5	3.6 (2.1 – 6.1)	24.0	3.7 (2.3 – 5.9)	30.0	3.6 (2.1 – 6.1)	28.0
1996	3.4 (2.3 – 4.9)	36.0	1.9 (0.8 – 4.0)	30.0	3.7 (2.4 – 5.6)	42.0	2.7 (1.4 – 5.0)	48.0	4.9 (3.2 – 7.3)	36.0	4.2 (2.5 – 6.9)	36.0
Onset within 24 hrs	0.8 (0.6 – 1.2)	34.3	0.7 (0.4 – 1.3)	25.5	0.9 (0.6 – 1.4)	33.5	0.8 (0.5 – 1.4)	32.0	1.1 (0.7 – 1.7)	37.0	0.8 (0.4 – 1.4)	33.0

Unk = unknown, NA = not applicable.
For numbers of participants for each dose and by birth cohort see chapter 5 - Table 9.
[1]$p < 0.05$ for trend in comparison of birth cohorts.

Table A7.2 Proportions of reported other symptoms within seven days after immunisation by birth cohort

Location of other symptom(s)	1st dose		2nd dose		3rd dose	
	All participants % (95% CI)	Complete responders % (95% CI)	All participants % (95% CI)	Complete responders % (95% CI)	All participants % (95% CI)	Complete responders % (95% CI)
On the arms	1.9 (1.5 – 2.4)	1.8 (1.3 – 2.6)	1.1 (0.8 – 1.5)	1.6 (1.1 – 2.4)	0.9 (0.6 – 1.2)	1.6 (1.1 – 2.4)
1993	2.0 (1.3 – 3.1)	2.2 (1.1 – 4.1)	1.5 (0.8 – 2.7)	1.5 (0.7 – 3.3)	2.3 (1.3 – 4.0)	2.0 (1.0 – 3.8)
1994	2.0 (1.3 – 3.1)	2.0 (1.0 – 3.8)	1.7 (0.9 – 3.0)	1.8 (0.8 - 3.6)	1.6 (0.8 – 3.1)	1.3 (0.5 – 3.0)
1995	2.0 (1.3 – 3.2)	1.8 (0.8 – 3.9)	1.4 (0.7 - 2.8)	1.3 (0.5 – 3.2)	1.6 (0.7 – 3.2)	2.1 (1.0 – 4.2)
1996	1.6 (0.9 – 2.8)	1.3 (0.5 – 3.2)	2.1 (1.2 – 3.6)	1.9 (0.8 – 4.0)	1.0 (0.4 – 2.5)	1.1 (0.3 - 2.9)
On other parts of the body	1.0 (0.7 – 1.4)	0.8 (0.4 – 1.4)	0.3 (0.2 – 0.5)	0.3 (0.1 – 0.7)	0.2 (0.1 – 0.4)	0.2 (0.1 – 0.7)
1993	1.2 (0.7 – 2.1)	1.5 (0.7 – 3.3)	0.7 (0.2 – 1.7)	0.4 (0.1 – 1.8)	0.5 (0.1 – 1.7)	0.4 (0.1 – 1.8)
1994	0.8 (0.4 – 1.6)	0.4 (0.1 – 1.7)	0.3 (0.0 – 1.1)	0.0 (0.0 – 1.0)	0.2 (0.0 – 1.2)	0.0 (0.0 – 1.0)
1995	1.0 (0.5 – 1.9)	0.5 (0.1 – 2.1)	0.5 (0.1 – 1.5)	0.5 (0.1 – 2.1)	0.4 (0.1 – 1.6)	0.3 (0.0 – 1.7)
1996	0.9 (0.4 – 1.9)	0.5 (0.1 – 2.1)	0.3 (0.1 – 1.3)	0.3 (0.0 - 1.7)	0.2 (0.0 – 1.3)	0.3 (0.0 – 1.7)
Other	1.6 (1.2 – 2.1)	1.2 (0.7 – 1.9)	0.7 (0.5 – 1.0)	1.0 (0.6 – 1.6)	0.6 (0.4 – 0.9)	1.1 (0.7 – 1.7)
1993	1.5 (0.9 – 2.5)	0.9 (0.3 – 2.4)	0.8 (0.3 – 1.8)	1.1 (0.4 – 2.7)	1.4 (0.7 – 2.9)	0.9 (0.3 – 2.4)
1994	1.5 (0.9 – 2.5	1.3 (0.5 – 3.0)	1.4 (0.7 – 2.6)	1.5 (0.7 – 3.3)	0.7 (0.2 – 2.0)	0.9 (0.3 – 2.4)
1995	1.7 (1.0 – 2.8)	0.8 (0.2 – 2.4)	0.9 (0.4 – 2.1)	0.5 (0.1 – 2.1)	1.0 (0.4 – 2.4)	1.3 (0.5 – 3.2)
1996	1.7 (1.0 – 2.9)	1.9 (0.8 – 4.0)	1.0 (0.4 – 2.2)	0.5 (0.1 – 2.1)	1.2 (0.5 – 2.8)	1.1 (0.3 – 2.9)

For numbers of participants for each dose and by birth cohort see chapter 5 - Table 9.
[1]$p < 0.05$ for trend in comparison of birth cohorts.

Appendix 8 Survey on tolerability – Modelling adverse events

Table A8.1 Modelling variation in events between participants and differences between birth cohort and dose

Event	Variation between participants	SE	1993[1] OR (95% CI)	1994[1] OR (95% CI)	1995[1] OR (95% CI)	2nd dose[2] OR (95% CI)	3rd dose[2] OR (95% CI)
AEs total	1.231	0.133	1.59 (1.19 – 2.12)	1.22 (0.92 – 1.61)	1.19 (0.89 – 1.58)	0.22 (0.17 – 0.28)	0.28 (0.21 – 0.36)
Local reactions	1.120	0.092	1.45 (1.18 – 1.79)	1.13 (0.93 – 1.39)	1.14 (0.92 – 1.41)	0.33 (0.28 – 0.38)	0.43 (0.37 – 0.51)
Swelling	1.197	0.088	1.45 (1.19 – 1.76)	1.25 (1.03 – 1.53)	0.94 (0.76 – 1.16)	0.93 (0.81 – 1.08)	1.35 (1.16 – 1.55)
Redness	0.974	0.085	1.13 (0.92 – 1.37)	1.17 (0.96 – 1.42)	1.04 (0.85 – 1.28)	1.06 (0.92 – 1.22)	0.95 (0.81 – 1.11)
Pain	1.041	0.078	1.31 (1.10 – 1.56)	1.26 (1.06 – 1.50)	1.20 (1.00 – 1.44)	0.47 (0.41 – 0.53)	0.57 (0.49 – 0.65)
Swelling in the armpit	1.448	0.310	1.49 (0.89 – 2.50)	1.34 (0.79 – 2.28)	1.14 (0.65 – 1.99)	0.63 (0.42 – 0.95)	0.60 (0.38 – 0.96)
Reduced use of the arm	0.954	0.069	1.08 (0.92 – 1.26)	0.98 (0.84 – 1.15)	1.06 (0.90 – 1.25)	0.36 (0.33 – 0.40)	0.42 (0.37 – 0.47)
Systemic AEs	1.071	0.088	1.41 (1.16 – 1.72)	1.32 (1.08 – 1.60)	1.27 (1.03 – 1.55)	0.33 (0.28 – 0.38)	0.32 (0.27 – 0.38)
Fever (≥ 38 °C)	0.885	0.185	0.93 (0.67 – 1.29)	0.86 (0.61 – 1.20)	0.93 (0.66 – 1.30)	0.64 (0.48 – 0.85)	0.97 (0.74 – 1.28)
Listlessness	1.084	0.091	1.21 (0.99 – 1.48)	1.38 (1.13 – 1.69)	1.14 (0.92 – 1.40)	0.60 (0.52 – 0.69)	0.51 (0.44 – 0.61)
Crying	1.243	0.166	1.32 (0.94 – 1.85)	1.48 (1.06 – 2.07)	1.12 (0.78 – 1.61)	0.85 (0.66 – 1.09)	0.87 (0.66 – 1.14)
Cold	0.550	0.071	1.10 (0.92 – 1.30)	1.13 (0.95 – 1.35)	1.17 (0.98 – 1.40)	0.63 (0.55 – 0.72)	1.14 (0.99 – 1.30)
Cough	0.575	0.100	1.17 (0.94 – 1.45)	1.20 (0.97 – 1.49)	1.03 (0.82 – 1.30)	0.72 (0.60 – 0.86)	1.14 (0.96 – 1.36)
Shortness of breath	1.143	0.135	1.61 (1.22 – 2.12)	1.17 (0.87 – 1.57)	1.17 (0.86 – 1.57)	0.60 (0.48 – 0.74)	0.68 (0.54 – 0.86)
Fatigue	1.118	0.080	1.48 (1.24 – 1.77)	1.43 (1.20 – 1.71)	1.24 (1.20 – 1.71)	0.52 (0.46 – 0.59)	0.59 (0.52 – 0.67)
Sleeping problems	1.082	0.105	1.42 (1.13 – 1.77)	1.13 (0.90 – 1.43)	1.14 (0.90 – 1.45)	0.52 (0.43 – 0.61)	0.51 (0.43 – 0.62)
Nausea	0.758	0.092	1.20 (0.97 – 1.47)	1.29 (0.97 – 1.47)	1.13 (0.91 – 1.40)	0.47 (0.40 – 0.55)	0.49 (0.41 – 0.58)
Vomiting	0.470	0.532	1.76 (0.98 – 3.15)	1.40 (0.76 – 2.58)	2.01 (1.12 – 3.60)	0.67 (0.43 – 1.05)	0.77 (0.49 – 1.23)
Diarrhoea	0.718	0.169	1.71 (1.23 – 2.38)	1.74 (1.25 – 2.43)	1.36 (0.96 – 1.93)	0.65 (0.51 – 0.84)	0.76 (0.59 – 0.99)
Abdominal pain	0.892	0.088	0.89 (0.72 – 1.08)	1.12 (0.92 – 1.36)	1.10 (0.90 – 1.34)	0.52 (0.45 – 0.61)	0.55 (0.47 – 0.65)
Headache	0.852	0.073	1.24 (1.05 – 1.48)	1.28 (1.08 – 1.53)	1.24 (1.04 – 1.47)	0.50 (0.44 – 0.56)	0.59 (0.52 – 0.67)

Table A8.1 continuing on the next page

Table A8.1 – Continued

Event	Variation between participants	SE	1993[1] OR (95% CI)	1994[1] OR (95% CI)	1995[1] OR (95% CI)	2nd dose[2] OR (95% CI)	3rd dose[2] OR (95% CI)
Systemic AEs							
Dizziness	0.856	0.088	1.18 (0.97 – 1.44)	1.23 (1.01 – 1.50)	1.18 (0.96 – 1.45)	0.41 (0.36 – 0.48)	0.41 (0.35 – 0.49)
Fainting	0.693	0.765	2.02 (0.99 – 4.10)	1.70 (0.82 – 3.53)	0.77 (0.32 – 1.86)	0.35 (0.18 – 0.68)	0.54 (0.29 – 0.99)
Myalgia	0.947	0.072	1.41 (1.20 – 1.66)	1.27 (1.08 – 1.50)	1.29 (1.09 – 1.53)	0.38 (0.34 – 0.43)	0.39 (0.35 – 0.44)
Joint pain	0.951	0.114	1.03 (0.81 – 1.31)	1.14 (0.90 – 1.45)	1.07 (0.83 – 1.36)	0.38 (0.31 – 0.46)	0.33 (0.26 – 0.41)
Muscle contractions	0.929	0.117	1.12 (0.88 – 1.43)	1.19 (0.93 – 1.52)	1.14 (0.88 – 1.46)	0.38 (0.32 – 0.47)	0.33 (0.26 – 0.41)
Sweating	0.975	0.186	1.39 (0.97 – 1.99)	1.52 (1.06 – 2.17)	1.40 (0.97 – 2.02)	0.51 (0.38 – 0.67)	0.52 (0.39 – 0.71)
Rash	0.899	0.148	1.29 (0.97 – 1.73)	1.05 (0.77 – 1.42)	1.20 (0.89 – 1.62)	0.72 (0.57 – 0.90)	0.61 (0.47 – 0.79)
Itch	1.172	0.113	1.01 (0.79 – 1.30)	1.05 (0.82 – 1.34)	0.94 (0.73 – 1.21)	0.66 (0.55 – 0.79)	0.60 (0.49 – 0.74)
Other symptoms	0.719	0.190	1.14 (0.83 – 1.58)	1.00 (0.72 – 1.40)	1.04 (0.74 – 1.46)	0.69 (0.53 – 0.89)	0.67 (0.50 – 0.89)
Absency							
School	0.623	0.126	1.09 (0.85 – 1.40)	1.13 (0.88 – 1.46)	1.14 (0.88 – 1.47)	0.45 (0.36 – 0.56)	0.81 (0.67 – 0.99)
Sport	0.701	0.123	0.95 (0.74 – 1.22)	0.96 (0.75 – 1.23)	1.08 (0.84 – 1.39)	0.44 (0.35 – 0.54)	0.51 (0.41 – 0.64)
Other activities	0.982	0.280	2.23 (1.38 – 3.62)	1.55 (0.93 – 2.59)	2.04 (1.24 – 3.36)	0.42 (0.29 – 0.61)	0.53 (0.36 – 0.78)
Parent/guardian from work	1.274	0.350	0.51 (0.30 – 0.86)	0.59 (0.36 – 0.99)	0.82 (0.51 – 1.33)	0.41 (0.26 – 0.66)	0.37 (0.22 – 0.63)
Use of analgesics	0.981	0.092	1.11 (0.90 – 1.36)	1.04 (0.84 – 1.28)	1.14 (0.92 – 1.42)	0.60 (0.51 – 0.71)	0.69 (0.58 – 0.82)
Medical intervention	0.548	0.543	1.19 (0.72 – 1.96)	0.75 (0.72 – 1.96)	0.59 (0.32 – 1.09)	0.63 (0.40 – 1.01)	0.69 (0.42 – 1.13)

[1]reference category = 1996.
[2]reference category = 1st dose.

Appendix 9 Survey on tolerability – Association between adverse events

Table A9.1 Association between local reactions (corrected for dose and birth cohort)

Adverse event	Swelling		Redness		Pain		Swelling in the armpit		Reduced use of the arm	
	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance
Swelling			0.16 (0.14 – 0.18)	< 0.001	0.27 (0.22 – 0.33)	< 0.001	0.22 (0.14 – 0.32)	< 0.001	0.36 (0.31 – 0.42)	< 0.001
Redness	0.16 (0.14 – 0.18)	< 0.001			0.25 (0.20 – 0.32)	< 0.001	0.24 (0.16 – 0.36)	< 0.001	0.44 (0.38 – 0.51)	< 0.001
Pain	0.27 (0.22 – 0.33)	< 0.001	0.26 (0.21 – 0.32)	< 0.001			0.18 (0.08 – 0.42)	< 0.001	0.25 (0.22 – 0.29)	< 0.001
Swelling in the armpit	0.21 (0.15 – 0.30)	< 0.001	0.25 (0.17 – 0.35)	< 0.001	0.18 (0.08 – 0.40)	< 0.001			0.17 (0.10 – 0.30)	< 0.001
Reduced use of the arm	0.36 (0.31 – 0.42)	< 0.001	0.44 (0.37 – 0.51)	< 0.001	0.25 (0.22 – 0.28)	< 0.001	0.18 (0.10 – 0.33)	< 0.001		

[1]reference category = presence of the adverse event.

Table A9.2 Association between local reactions and systemic AEs (corrected for dose and birth cohort)

Adverse event	Fever (> 38 °C)		Listlessness		Crying		Cold	
	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance
Swelling	0.74 (0.54 – 0.99)	0.049	0.52 (0.44 – 0.61)	< 0.001	0.49 (0.38 – 0.65)	< 0.001	0.67 (0.57 – 0.77)	< 0.001
Redness	0.58 (0.43 – 0.77)	< 0.001	0.47 (0.40 – 0.55)	< 0.001	0.56 (0.42 – 0.74)	< 0.001	0.57 (0.49 – 0.66)	< 0.001
Pain	0.59 (0.41 – 0.83)	0.002	0.39 (0.32 – 0.47)	< 0.001	0.45 (0.32 – 0.65)	< 0.001	0.48 (0.41 – 0.57)	< 0.001
Swelling in the armpit	0.30 (0.17 – 0.53)	< 0.001	0.18 (0.12 – 0.26)	< 0.001	0.35 (0.19 – 0.62)	< 0.001	0.33 (0.23 – 0.47)	< 0.001
Reduced use of the arm	0.45 (0.34 – 0.61)	< 0.001	0.31 (0.27 – 0.37)	< 0.001	0.46 (0.34 – 0.61)	< 0.001	0.59 (0.52 – 0.68)	< 0.001

Adverse event	Cough		Shortness of breath		Fatigue		Sleeping problems		Nausea	
	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance
Swelling	0.55 (0.46 – 0.67)	< 0.001	0.44 (0.35 – 0.55)	< 0.001	0.45 (0.39 – 0.52)	< 0.001	0.43 (0.36 – 0.51)	< 0.001	0.53 (0.44 – 0.63)	< 0.001
Redness	0.49 (0.41 – 0.59)	< 0.001	0.39 (0.31 – 0.48)	< 0.001	0.48 (0.42 – 0.56)	< 0.001	0.44 (0.37 – 0.53)	< 0.001	0.53 (0.45 – 0.64)	< 0.001
Pain	0.53 (0.42 – 0.66)	< 0.001	0.38 (0.28 – 0.52)	< 0.001	0.40 (0.34 – 0.46)	< 0.001	0.32 (0.25 – 0.41)	< 0.001	0.44 (0.35 – 0.55)	< 0.001
Swelling in the armpit	0.24 (0.16 – 0.35)	< 0.001	0.18 (0.11 – 0.27)	< 0.001	0.21 (0.14 – 0.31)	< 0.001	0.21 (0.14 – 0.31)	< 0.001	0.26 (0.18 – 0.39)	< 0.001
Reduced use of the arm	0.56 (0.47 – 0.66)	< 0.001	0.39 (0.31 – 0.50)	< 0.001	0.35 (0.31 – 0.40)	< 0.001	0.34 (0.28 – 0.41)	< 0.001	0.46 (0.38 – 0.54)	< 0.001

Table A9.2 continuing on the next page

Table A9.2 - Continued

Adverse event	Vomiting		Diarrhoea		Abdominal pain		Headache		Dizziness	
	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance
Swelling	0.69 (0.42 – 1.14)	0.149	0.57 (0.44 – 0.75)	< 0.001	0.48 (0.40 – 0.56)	< 0.001	0.50 (0.44 – 0.58)	< 0.001	0.42 (0.36 – 0.50)	< 0.001
Redness	0.47 (0.30 – 0.75)	0.001	0.47 (0.36 – 0.61)	< 0.001	0.43 (0.36 – 0.50)	< 0.001	0.46 (0.40 – 0.53)	< 0.001	0.46 (0.39 – 0.54)	< 0.001
Pain	1.10 (0.67 – 1.80)	0.708	0.68 (0.49 – 0.92)	0.014	0.46 (0.38 – 0.56)	< 0.001	0.45 (0.38 – 0.52)	< 0.001	0.38 (0.31 – 0.47)	< 0.001
Swelling in the armpit	0.21 (0.09 – 0.45)	< 0.001	0.32 (0.19 – 0.54)	< 0.001	0.27 (0.18 – 0.39)	< 0.001	0.31 (0.22 – 0.45)	< 0.001	0.26 (0.18 – 0.37)	< 0.001
Reduced use of the arm	0.62 (0.40 – 0,98)	0.039	0.56 (0.43 – 0.72)	< 0.001	0.46 (0.39 – 0.54)	< 0.001	0.44 (0.38 – 0.50)	< 0.001	0.38 (0.32 – 0.44)	< 0.001

Adverse event	Fainting		Myalgia		Joint pain		Muscle contractions	
	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance
Swelling	0.48 (0.27 – 0.86)	0.013	0.55 (0.47 – 0.64)	< 0.001	0.44 (0.36 – 0.54)	< 0.001	0.47 (0.38 – 0.58)	< 0.001
Redness	0.92 (0.47 – 1.80)	0.798	0.62 (0.53 – 0.72)	< 0.001	0.49 (0.40 – 0.59)	< 0.001	0.59 (0.47 – 0.72)	< 0.001
Pain	0.47 (0.20 – 1.10)	0.081	0.37 (0.33 – 0.42)	< 0.001	0.35 (0.26 – 0.46)	< 0.001	0.32 (0.24 – 0.43)	< 0.001
Swelling in the armpit	0.16 (0.07 – 0.39)	< 0.001	0.32 (0.19 – 0.54)	< 0.001	0.19 (0.13 – 0.28)	< 0.001	0.21 (0.14 – 0.32)	< 0.001
Reduced use of the arm	0.43 (0.22 – 0.83)	0.012	0.30 (0.27 – 0.33)	< 0.001	0.25 (0.20 – 0,32)	< 0.001	0.34 (0.27 – 0.42)	< 0.001

Adverse event	Sweating		Rash		Itch		Other symptoms	
	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance
Swelling	0.57 (0.42 – 0.76)	< 0.001	0.33 (0.26 – 0.42)	< 0.001	0.42 (0.35 – 0.52)	< 0.001	0.45 (0.34 – 0.59)	< 0.001
Redness	0.59 (0.44 – 0.79)	< 0.001	0.24 (0.19 – 0.30)	< 0.001	0.35 (0.29 – 0.43)	< 0.001	0.51 (0.38 – 0.67)	< 0.001
Pain	0.70 (0.50 – 0.99)	0.042	0.34 (0.24 – 0.49)	< 0.001	0.48 (0.38 – 0.62)	< 0.001	0.58 (0.41 – 0.83)	0.003
Swelling in the armpit	0.21 (0.13 – 0.35)	< 0.001	0.20 (0.13 – 0.30)	< 0.001	0.30 (0.20 – 0.47)	< 0.001	0.29 (0.17 – 0.50)	< 0.001
Reduced use of the arm	0.51 (0.38 – 0.69)	< 0.001	0.47 (0.37 - 0.60)	< 0.001	0.44 (0.36 – 0.54)	< 0.001	0.54 (0.41 – 0.72)	< 0.001

Table A9.2 continuing on the next page

Table A9.2 - Continued

Adverse event	Swelling		Redness		Pain		Swelling in the armpit		Reduced use of the arm	
	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance
Fever (> 38 °C)	0.70 (0.53 – 0.93)	0.013	0.56 (0.42 – 0.74)	< 0.001	0.58 (0.41 – 0.80)	0.001	0.30 (0.17 – 0.53)	< 0.001	0.44 (0.33 – 0.58)	< 0.001
Listlessness	0.52 (0.44 – 0.61)	< 0.001	0.48 (0.40 – 0.56)	< 0.001	0.39 (0.32 – 0.47)	< 0.001	0.18 (0.12 – 0.28)	< 0.001	0.32 (0.27 – 0.37)	< 0.001
Crying	0.49 (0.38 – 0.63)	< 0.001	0.56 (0.43 – 0.73)	< 0.001	0.44 (0.31 – 0.63)	< 0.001	0.34 (0.19 – 0.63)	< 0.001	0.46 (0.56 – 0.60)	< 0.001
Cold	0.64 (0.56 – 0.74)	< 0.001	0.56 (0.49 – 0.65)	< 0.001	0.47 (0.40 – 0.55)	< 0.001	0.32 (0.22 – 0.48)	< 0.001	0.58 (0.51 – 0.66)	< 0.001
Cough	0.53 (0.44 – 0.63)	< 0.001	0.48 (0.40 – 0.57)	< 0.001	0.52 (0.42 – 0.64)	< 0.001	0.23 (0.15 – 0.35)	< 0.001	0.54 (0.46 – 0.64)	< 0.001
Shortness of breath	0.43 (0.35 – 0.53)	< 0.001	0.39 (0.31 – 0.48)	< 0.001	0.38 (0.28 – 0.51)	< 0.001	0.18 (0.11 – 0.28)	< 0.001	0.38 (0.31 – 0.48)	< 0.001
Fatigue	0.45 (0.39 – 0.52)	< 0.001	0.49 (0.43 – 0.57)	< 0.001	0.40 (0.34 – 0.46)	< 0.001	0.21 (0.13 – 0.33)	< 0.001	0.36 (0.32 – 0.40)	< 0.001
Sleeping problems	0.43 (0.36 – 0.51)	< 0.001	0.44 (0.37 – 0.53)	< 0.001	0.32 (0.25 – 0.41)	< 0.001	0.21 (0.14 – 0.33)	< 0.001	0.34 (0.28 – 0.41)	< 0.001
Nausea	0.52 (0.44 – 0.61)	< 0.001	0.52 (0.44 – 0.62)	< 0.001	0.42 (0.34 – 0.52)	< 0.001	0.26 (0.17 – 0.39)	< 0.001	0.44 (0.38 – 0.52)	< 0.001
Vomiting	0.70 (0.45 – 1.10)	0.122	0.48 (0.31 – 0.72)	< 0.001	1.01 (0.64 – 1.59)	0.962	0.20 (0.10 – 0.43)	< 0.001	0.61 (0.40 – 0.93)	0.020
Diarrhoea	0.55 (0.43 – 0.70)	< 0.001	0.45 (0.36 – 0.58)	< 0.001	0.65 (0.49 – 0.87)	0.004	0.30 (0.18 – 0.52)	< 0.001	0.55 (0.43 – 0.70)	< 0.001
Abdominal pain	0.47 (0.40 – 0.55)	< 0.001	0.43 (0.36 – 0.50)	< 0.001	0.45 (0.37 – 0.55)	< 0.001	0.27 (0.18 – 0.40)	< 0.001	0.45 (0.39 – 0.52)	< 0.001
Headache	0.49 (0.43 – 0.57)	< 0.001	0.46 (0.40 – 0.53)	< 0.001	0.44 (0.38 – 0.51)	< 0.001	0.30 (0.21 – 0.45)	< 0.001	0.43 (0.38 – 0.49)	< 0.001
Dizziness	0.42 (0.36 – 0.49)	< 0.001	0.46 (0.39 – 0.54)	< 0.001	0.37 (0.30 – 0.45)	< 0.001	0.25 (0.17 – 0.38)	< 0.001	0.37 (0.32 – 0.43)	< 0.001
Fainting	0.43 (0.26 – 0.71)	0.001	0.84 (0.45 – 1.57)	0.576	0.45 (0.21 – 1.00)	0.050	0.15 (0.07 – 0.34)	< 0.001	0.40 (0.22 – 0.74)	0.004
Myalgia	0.55 (0.47 – 0.64)	< 0.001	0.62 (0.53 – 0.72)	< 0.001	0.37 (0.33 – 0.42)	< 0.001	0.31 (0.18 – 0.55)	< 0.001	0.30 (0.27 – 0.33)	< 0.001
Joint pain	0.44 (0.36 – 0.53)	< 0.001	0.48 (0.39 – 0.58)	< 0.001	0.33 (0.25 – 0.44)	< 0.001	0.19 (0.12 – 0.29)	< 0.001	0.25 (0.20 – 0.31)	< 0.001
Muscle contractions	0.46 (0.38 – 0.56)	< 0.001	0.58 (0.47 – 0.71)	< 0.001	0.31 (0.23 – 0.41)	< 0.001	0.21 (0.13 – 0.32)	< 0.001	0.33 (0.26 – 0.40)	< 0.001
Sweating	0.55 (0.42 – 0.72)	< 0.001	0.58 (0.44 – 0.77)	< 0.001	0.65 (0.47 – 0.90)	< 0.001	0.20 (0.12 – 0.34)	< 0.001	0.48 (0.36 – 0.63)	< 0.001
Rash	0.32 (0.26 – 0.40)	< 0.001	0.24 (0.19 – 0.29)	< 0.001	0.33 (0.24 – 0.47)	< 0.001	0.19 (0.12 – 0.30)	< 0.001	0.47 (0.37 – 0.59)	< 0.001
Itch	0.43 (0.35 – 0.52)	< 0.001	0.36 (0.29 – 0.43)	< 0.001	0.49 (0.38 – 0.62)	< 0.001	0.29 (0.18 – 0.46)	< 0.001	0.44 (0.36 – 0.53)	< 0.001
Other symptoms	0.45 (0.35 – 0.58)	< 0.001	0.49 (0.38 – 0.64)	< 0.001	0.55 (0.40 – 0.77)	< 0.001	0.28 (0.16 – 0.48)	< 0.001	0.54 (0.41 – 0.70)	< 0.001

[1]reference category = presence of the adverse event.

Table A9.3 Association between systemic AEs (corrected for dose and birth cohort)

Adverse event	Fever (> 38 °C)		Listlessness		Crying		Cold	
	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance
Fever (> 38 °C)			0.17 (0.13 – 0.22)	< 0.001	0.21 (0.15 – 0.30)	< 0.001	0.17 (0.13 – 0.21)	< 0.001
Listlessness	0.17 (0.13 - 0.22)	< 0.001			0.11 (0.08 – 0.14)	< 0.001	0.30 (0.26 – 0.35)	< 0.001
Crying	0.22 (0.15 – 0.32)	< 0.001	0.11 (0.08 – 0.14)	< 0.001			0.32 (0.25 – 0.41)	< 0.001
Cold	0.16 (0.13 – 0.21)	< 0.001	0.30 (0.26 – 0.34)	< 0.001	0.31 (0.24 – 0.40)	< 0.001		
Cough	0.13 (0.10 – 0.17)	< 0.001	0.26 (0.22 – 0.31)	< 0.001	0.33 (0.25 – 0.44)	< 0.001	0.04 (0.04 – 0.05)	< 0.001
Shortness of breath	0.12 (0.09 – 0.16)	< 0.001	0.31 (0.11 – 0.16)	< 0.001	0.18 (0.13 – 0.24)	< 0.001	0.20 (0.16 – 0.24)	< 0.001
Fatigue	0.15 (0.11 – 0.21)	< 0.001	0.04 (0.03 – 0.04)	< 0.001	0.11 (0.08 – 0.14)	< 0.001	0.23 (0.20 – 0.27)	< 0.001
Sleeping problems	0.18 (0.14 – 0.25)	< 0.001	0.13 (0.11 – 0.16)	< 0.001	0.17 (0.13 – 0.22)	< 0.001	0.35 (0.30 – 0.42)	< 0.001
Nausea	0.16 (0.12 – 0.21)	< 0.001	0.21 (0.18 – 0.24)	< 0.001	0.31 (0.24 – 0.40)	< 0.001	0.40 (0.35 – 0.47)	< 0.001
Vomiting	0.08 (0.05 – 0.11)	< 0.001	0.35 (0.23 – 0.53)	< 0.001	0.48 (0.24 – 0.97)	0.040	0.49 (0.33 – 0.73)	< 0.001
Diarrhoea	0.26 (0.18 – 0.38)	< 0.001	0.28 (0.22 – 0.36)	< 0.001	0.34 (0.24 – 0.50)	< 0.001	0.45 (0.36 – 0.56)	< 0.001
Abdominal pain	0.20 (0.15 – 0.26)	< 0.001	0.19 (0.17 – 0.23)	< 0.001	0.27 (0.21 – 0.34)	< 0.001	0.36 (0.31 – 0.42)	< 0.001
Headache	0.12 (0.09 – 0.16)	< 0.001	0.18 (0.16 – 0.21)	< 0.001	0.25 (0.19 – 0.31)	< 0.001	0.31 (0.27 – 0.35)	< 0.001
Dizziness	0.15 (0.12 – 0.20)	< 0.001	0.16 (0.14 – 0.19)	< 0.001	0.21 (0.17 – 0.28)	< 0.001	0.36 (0.31 – 0.42)	< 0.001
Fainting	0.07 (0.04 – 0.11)	< 0.001	0.27 (0.16 – 0.45)	< 0.001	0.15 (0.08 – 0.28)	< 0.001	0.33 (0.20 – 0.54)	< 0.001
Myalgia	0.73 (0.54 – 0.97)	0.030	0.49 (0.42 – 0.57)	< 0.001	0.64 (0.48 - 0.85)	0.002	0.83 (0.73 – 0.95)	0.008
Joint pain	0.31 (0.23 – 0.43)	< 0.001	0.24 (0.20 – 0.29)	< 0.001	0.33 (0.24 – 0.45)	< 0.001	0.49 (0.41 – 0.59)	< 0.001
Muscle contractions	0.61 (0.42 – 0.88)	0.009	0.34 (0.28 – 0.41)	< 0.001	0.38 (0.27 – 0.52)	< 0.001	0.69 (0.57 – 0.84)	< 0.001
Sweating	0.28 (0.19 – 0.42)	< 0.001	0.20 (0.16 – 0.26)	< 0.001	0.21 (0.14 – 0.30)	< 0.001	0.42 (0.33 – 0.54)	< 0.001
Rash	0.39 (0.27 – 0.57)	< 0.001	0.31 (0.25 – 0.39)	< 0.001	0.40 (0.28 – 0.57)	< 0.001	0.40 (0.32 – 0.50)	< 0.001
Itch	0.69 (0.47 – 1.01)	0.054	0.34 (0.28 – 0.41)	< 0.001	0.38 (0.27 – 0.52)	< 0.001	0.71 (0.59 – 0.86)	< 0.001
Other symptoms	0.35 (0.23 – 0.52)	< 0.001	0.40 (0.31 – 0.52)	< 0.001	0.41 (0.27 – 0.62)	< 0.001	0.65 (0.50 – 0.84)	0.001

Table A9.3 continuing on the next page

Table A9.3 - Continued

Adverse event	Cough		Shortness of breath		Fatigue		Sleeping problems		Nausea	
	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance
Fever (> 38 °C)	0.14 (0.11 – 0.17)	< 0.001	0.12 (0.09 – 0.16)	< 0.001	0.16 (0.21 – 0.21)	< 0.001	0.19 (0.15 – 0.25)	< 0.001	0.17 (0.13 – 0.21)	< 0.001
Listlessness	0.27 (0.22 – 0.32)	< 0.001	0.13 (0.10 – 0.16)	< 0.001	0.04 (0.03 – 0.04)	< 0.001	0.13 (0.10 – 0.16)	< 0.001	0.21 (0.17 – 0.25)	< 0.001
Crying	0.35 (0.26 – 0.46)	< 0.001	0.18 (0.13 – 0.24)	< 0.001	0.11 (0.08 – 0.14)	< 0.001	0.17 (0.13 – 0.22)	< 0.001	0.32 (0.24 – 0.41)	< 0.001
Cold	0.04 (0.04 – 0.05)	< 0.001	0.19 (0.16 – 0.23)	< 0.001	0.23 (0.20 – 0.26)	< 0.001	0.34 (0.29 – 0.40)	< 0.001	0.40 (0.35 – 0.47)	< 0.001
Cough			0.14 (0.11 – 0.18)	< 0.001	0.23 (0.20 – 0.27)	< 0.001	0.32 (0.27 – 0.39)	< 0.001	0.44 (0.36 – 0.53)	< 0.001
Shortness of breath	0.15 (0.12 – 0.18)	< 0.001			0.13 (0.10 – 0.16)	< 0.001	0.15 (0.12 – 0.19)	< 0.001	0.19 (0.16 – 0.24)	< 0.001
Fatigue	0.25 (0.21 – 0.29)	< 0.001	0.12 (0.10 – 0.16)	< 0.001			0.10 (0.08 – 0.12)	< 0.001	0.21 (0.18 – 0.24)	< 0.001
Sleeping problems	0.33 (0.27 – 0.41)	< 0.001	0.15 (0.12 – 0.19)	< 0.001	0.10 (0.08 – 0.12)	< 0.001			0.23 (0.19 – 0.27)	< 0.001
Nausea	0.44 (0.36 – 0.53)	< 0.001	0.19 (0.15 – 0.23)	< 0.001	0.21 (0.18 – 0.24)	< 0.001	0.22 (0.19 – 0.26)	< 0.001		
Vomiting	0.32 (0.21 – 0.50)	< 0.001	0.22 (0.14 – 0.34)	< 0.001	0.34 (0.23 – 0.49)	< 0.001	0.33 (0.21 – 0.51)	< 0.001	0.04 (0.02 – 0.06)	< 0.001
Diarrhoea	0.41 (0.31 – 0.53)	< 0.001	0.33 (0.24 – 0.45)	< 0.001	0.27 (0.22 – 0.34)	< 0.001	0.26 (0.20 – 0.33)	< 0.001	0.21 (0.17 – 0.26)	< 0.001
Abdominal pain	0.32 (0.27 – 0.38)	< 0.001	0.17 (0.14 – 0.21)	< 0.001	0.19 (0.16 – 0.22)	< 0.001	0.21 (0.18 – 0.25)	< 0.001	0.09 (0.08 – 0.11)	< 0.001
Headache	0.29 (0.24 – 0.34)	< 0.001	0.19 (0.15 – 0.23)	< 0.001	0.17 (0.15 – 0.19)	< 0.001	0.24 (0.20 – 0.28)	< 0.001	0.11 (0.09 – 0.13)	< 0.001
Dizziness	0.31 (0.26 – 0.37)	< 0.001	0.11 (0.09 – 0.14)	< 0.001	0.14 (0.12 – 0.16)	< 0.001	0.18 (0.15 – 0.21)	< 0.001	0.08 (0.07 – 0.09)	< 0.001
Fainting	0.28 (0.16 – 0.48)	< 0.001	0.09 (0.06 – 0.15)	< 0.001	0.24 (0.14 – 0.40)	< 0.001	0.22 (0.13 – 0.37)	< 0.001	0.13 (0.08 – 0.21)	< 0.001
Myalgia	0.84 (0.70 – 1.00)	0.053	0.54 (0.42 – 0.69)	< 0.001	0.58 (0.51 – 0.65)	< 0.001	0.53 (0.44 – 0.63)	< 0.001	0.55 (0.46 – 0.65)	< 0.001
Joint pain	0.45 (0.36 – 0.56)	< 0.001	0.27 (0.21 – 0.35)	< 0.001	0.27 (0.23 – 0.32)	< 0.001	0.24 (0.19 – 0.29)	< 0.001	0.36 (0.30 – 0.44)	< 0.001
Muscle contractions	0.57 (0.45 – 0.72)	< 0.001	0.38 (0.29 – 0.50)	< 0.001	0.34 (0.29 – 0.41)	< 0.001	0.30 (0.24 – 0.37)	< 0.001	0.50 (0.41 – 0.62)	< 0.001
Sweating	0.33 (0.25 – 0.45)	< 0.001	0.22 (0.16 – 0.30)	< 0.001	0.19 (0.15 – 0.25)	< 0.001	0.22 (0.17 – 0.29)	< 0.001	0.39 (0.30 – 0.51)	< 0.001
Rash	0.36 (0.28 – 0.47)	< 0.001	0.27 (0.21 – 0.36)	< 0.001	0.31 (0.26 – 0.39)	< 0.001	0.28 (0.22 – 0.36)	< 0.001	0.45 (0.35 – 0.57)	< 0.001
Itch	0.63 (0.50 – 0.80)	< 0.001	0.33 (0.25 – 0.42)	< 0.001	0.42 (0.35 – 0.50)	< 0.001	0.36 (0.29 – 0.44)	< 0.001	0.36 (0.30 – 0.44)	< 0.001
Other symptoms	0.54 (0.40 – 0.74)	< 0.001	0.36 (0.26 – 0.51)	< 0.001	0.42 (0.33 – 0.53)	< 0.001	0.36 (0.27 – 0.47)	< 0.001	0.41 (0.31 – 0.54)	< 0.001

Table A9.3 continuing on the next page

Table A9.3 - Continued

Adverse event	Vomiting		Diarrhoea		Abdominal pain		Headache		Dizziness	
	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance
Fever (> 38 °C)	0.07 (0.04 – 0.12)	< 0.001	0.27 (0.19 – 0.38)	< 0.001	0.20 (0.16 – 0.26)	< 0.001	0.13 (0.10 – 0.17)	< 0.001	0.16 (0.13 – 0.21)	< 0.001
Listlessness	0.33 (0.21 – 0.52)	< 0.001	0.29 (0.23 – 0.38)	< 0.001	0.19 (0.17 – 0.23)	< 0.001	0.18 (0.16 – 0.21)	< 0.001	0.16 (0.14 – 0.19)	< 0.001
Crying	0.48 (0.23 – 1.01)	0.053	0.36 (0.25 – 0.53)	< 0.001	0.27 (0.21 – 0.35)	< 0.001	0.26 (0.20 – 0.32)	< 0.001	0.22 (0.17 – 0.28)	< 0.001
Cold	0.48 (0.32 – 0.74)	< 0.001	0.46 (0.36 – 0.58)	< 0.001	0.35 (0.31 – 0.41)	< 0.001	0.30 (0.27 – 0.34)	< 0.001	0.36 (0.31 – 0.41)	< 0.001
Cough	0.32 (0.20 – 0.51)	< 0.001	0.41 (0.31 – 0.55)	< 0.001	0.31 (0.26 – 0.37)	< 0.001	0.28 (0.24 – 0.33)	< 0.001	0.30 (0.26 – 0.36)	< 0.001
Shortness of breath	0.22 (0.13 – 0.36)	< 0.001	0.35 (0.25 – 0.48)	< 0.001	0.17 (0.14 – 0.21)	< 0.001	0.19 (0.16 – 0.23)	< 0.001	0.11 (0.09 – 0.14)	< 0.001
Fatigue	0.34 (0.22 – 0.52)	< 0.001	0.29 (0.23 – 0.38)	< 0.001	0.19 (0.16 – 0.22)	< 0.001	0.17 (0.15 – 0.19)	< 0.001	0.14 (0.12 – 0.16)	< 0.001
Sleeping problems	0.35 (0.21 – 0.56)	< 0.001	0.27 (0.21 – 0.36)	< 0.001	0.21 (0.18 – 0.25)	< 0.001	0.24 (0.20 – 0.28)	< 0.001	0.18 (0.15 – 0.22)	< 0.001
Nausea	0.03 (0.02 – 0.05)	< 0.001	0.21 (0.16 – 0.27)	< 0.001	0.09 (0.08 – 0.11)	< 0.001	0.11 (0.09 – 0.13)	< 0.001	0.08 (0.07 – 0.09)	< 0.001
Vomiting			0.08 (0.05 – 0.12)	< 0.001	0.11 (0.07 – 0.16)	< 0.001	0.17 (0.11 – 0.25)	< 0.001	0.18 (0.13 – 0.27)	< 0.001
Diarrhoea	0.08 (0.05 – 0.12)	< 0.001			0.10 (0.08 – 0.13)	< 0.001	0.27 (0.22 – 0.34)	< 0.001	0.28 (0.22 – 0.35)	< 0.001
Abdominal pain	0.10 (0.06 – 0.15)	< 0.001	0.10 (0.08 – 0.13)	< 0.001			0.14 (0.12 – 0.16)	< 0.001	0.15 (0.13 – 0.18)	< 0.001
Headache	0.16 (0.10 – 0.25)	< 0.001	0.28 (0.22 – 0.36)	< 0.001	0.14 (0.12 – 0.16)	< 0.001			0.10 (0.09 – 0.12)	< 0.001
Dizziness	0.18 (0.12 – 0.27)	< 0.001	0.28 (0.22 – 0.36)	< 0.001	0.15 (0.13 – 0.18)	< 0.001	0.10 (0.09 – 0.11)	< 0.001		
Fainting	0.10 (0.04 – 0.22)	< 0.001	0.28 (0.14 – 0.56)	< 0.001	0.27 (0.16 – 0.44)	< 0.001	0.19 (0.11 - 0.32)	< 0.001	0.03 (0.02 – 0.07)	< 0.001
Myalgia	0.70 (0.44 – 1.12)	0.136	0.75 (0.57 – 0.98)	0.033	0.64 (0.55 – 0.75)	< 0.001	0.63 (0.56 – 0.72)	< 0.001	0.48 (0.41 – 0.57)	< 0.001
Joint pain	0.64 (0.36 – 1.15)	0.134	0.48 (0.35 – 0.65)	< 0.001	0.31 (0.26 – 0.38)	< 0.001	0.31 (0.26 – 0.37)	< 0.001	0.28 (0.23 – 0.33)	< 0.001
Muscle contractions	0.61 (0.34 – 1.12)	0.110	0.37 (0.27 – 0.51)	< 0.001	0.45 (0.37 – 0.55)	< 0.001	0.52 (0.43 – 0.62)	< 0.001	0.40 (0.33 – 0.49)	< 0.001
Sweating	0.37 (0.19 – 0.71)	0.003	0.23 (0.16 – 0.33)	< 0.001	0.27 (0.21 – 0.34)	< 0.001	0.34 (0.27 – 0.44)	< 0.001	0.24 (0.19 – 0.31)	< 0.001
Rash	0.53 (0.27 – 1.03)	0.060	0.27 (0.19 – 0.37)	< 0.001	0.29 (0.23 – 0.36)	< 0.001	0.36 (0.29 – 0.44)	< 0.001	0.34 (0.27 – 0.42)	< 0.001
Itch	0.72 (0.39 – 1.32)	0.287	0.41 (0.30 – 0.56)	< 0.001	0.34 (0.28 – 0.41)	< 0.001	0.38 (0.32 – 0.46)	< 0.001	0.33 (0.27 – 0.40)	< 0.001
Other symptoms	0.64 (0.29 – 1.42)	0.273	0.47 (0.31 – 0.71)	< 0.001	0.32 (0.25 – 0.41)	< 0.001	0.42 (0.34 – 0.54)	< 0.001	0.38 (0.30 – 0.50)	< 0.001

Table A9.3 continuing on the next page

Table A9.3 - Continued

Adverse event	Fainting		Myalgia		Joint pain		Muscle contractions	
	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance
Fever (> 38 °C)	0.07 (0.04 – 0.12)	< 0.001	0.72 (0.55 – 0.95)	0.018	0.32 (0.24 – 0.42)	< 0.001	0.61 (0.43 – 0.88)	0.007
Listlessness	0.28 (0.15 – 0.50)	< 0.001	0.49 (0.42 – 0.58)	< 0.001	0.25 (0.20 – 0.30)	< 0.001	0.34 (0.28 – 0.42)	< 0.001
Crying	0.16 (0.08 – 0.32)	< 0.001	0.64 (0.49 – 0.83)	< 0.001	0.34 (0.25 – 0.45)	< 0.001	0.38 (0.28 – 0.52)	< 0.001
Cold	0.34 (0.20 – 0.57)	< 0.001	0.82 (0.72 – 0.93)	0.002	0.49 (0.41 – 0.59)	< 0.001	0.69 (0.57 – 0.84)	< 0.001
Cough	0.30 (0.17 – 0.54)	< 0.001	0.82 (0.69 – 0.95)	0.017	0.44 (0.36 – 0.55)	< 0.001	0.56 (0.45 – 0.71)	< 0.001
Shortness of breath	0.10 (0.06 – 0.18)	< 0.001	0.54 (0.43 – 0.69)	< 0.001	0.28 (0.22 – 0.35)	< 0.001	0.39 (0.30 – 0.51)	< 0.001
Fatigue	0.26 (0.15 – 0.47)	< 0.001	0.58 (0.51 – 0.66)	< 0.001	0.27 (0.23 – 0.33)	< 0.001	0.35 (0.29 – 0.42)	< 0.001
Sleeping problems	0.24 (0.13 – 0.42)	< 0.001	0.53 (0.44 – 0.64)	< 0.001	0.24 (0.20 – 0.30)	< 0.001	0.30 (0.25 – 0.38)	< 0.001
Nausea	0.12 (0.07 – 0.22)	< 0.001	0.54 (0.46 – 0.64)	< 0.001	0.36 (0.30 – 0.44)	< 0.001	0.50 (0.41 – 0.62)	< 0.001
Vomiting	0.10 (0.04 – 0.22)	< 0.001	0.69 (0.45 – 1.06)	0.091	0.64 (0.37 – 1.10)	0.106	0.61 (0.35 – 1.06)	0.080
Diarrhoea	0.28 (0.14 – 0.57)	< 0.001	0.74 (0.58 – 0.94)	0.016	0.47 (0.34 – 0.63)	< 0.001	0.37 (0.28 – 0.50)	< 0.001
Abdominal pain	0.28 (0.16 – 0.49)	< 0.001	0.64 (0.55 – 0.75)	< 0.001	0.31 (0.26 – 0.38)	< 0.001	0.45 (0.37 – 0.55)	< 0.001
Headache	0.19 (0.11 – 0.33)	< 0.001	0.63 (0.56 – 0.71)	< 0.001	0.63 (0.56 – 0.71)	< 0.001	0.53 (0.44 – 0.64)	< 0.001
Dizziness	0.03 (0.02 – 0.07)	< 0.001	0.49 (0.41 – 0.57)	< 0.001	0.28 (0.23 – 0.34)	< 0.001	0.40 (0.33 – 0.49)	< 0.001
Fainting			0.49 (0.26 – 0.92)	0.026	0.47 (0.25 – 0.89)	0.019	0.39 (0.21 – 0.72)	0.003
Myalgia	0.49 (0.25 – 0.97)	0.041			0.13 (0.09 – 0.17)	< 0.001	0.18 (0.14 – 0.24)	< 0.001
Joint pain	0.47 (0.24 – 0.92)	0.028	0.13 (0.09 – 0.17)	< 0.001			0.13 (0.10 – 0.16)	< 0.001
Muscle contractions	0.39 (0.20 – 0.76)	0.005	0.18 (0.14 – 0.24)	< 0.001	0.13 (0.10 – 0.15)	< 0.001		
Sweating	0.32 (0.14 – 0.71)	0.005	0.50 (0.38 – 0.68)	< 0.001	0.24 (0.18 – 0.33)	< 0.001	0.22 (0.17 – 0.30)	< 0.001
Rash	0.49 (0.22 – 1.14)	0.097	0.45 (0.35 – 0.58)	< 0.001	0.37 (0.28 – 0.48)	< 0.001	0.37 (0.28 – 0.49)	< 0.001
Itch	0.37 (0.19 – 0.73)	0.004	0.30 (0.24 – 0.38)	< 0.001	0.35 (0.28 – 0.44)	< 0.001	0.35 (0.28 – 0.44)	< 0.001
Other symptoms	0.19 (0.10 – 0.38)	< 0.001	0.63 (0.48 – 0.83)	< 0.001	0.41 (0.30 – 0.55)	< 0.001	0.46 (0.34 – 0.64)	< 0.001

Table A9.3 continuing on the next page

Table A9.3 - Continued

Adverse event	Sweating		Rash		Itch		Other symptoms	
	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance	OR[1] (95% CI)	significance
Fever (> 38 °C)	0.28 (0.19 – 0.42)	< 0.001	0.39 (0.27 – 0.56)	< 0.001	0.69 (0.48 – 0.99)	0.045	0.35 (0.23 – 0.53)	< 0.001
Listlessness	0.21 (0.16 – 0.27)	< 0.001	0.32 (0.25 – 0.41)	< 0.001	0.34 (0.27 – 0.41)	< 0.001	0.42 (0.31 – 0.56)	< 0.001
Crying	0.21 (0.15 – 0.31)	< 0.001	0.41 (0.29 – 0.60)	< 0.001	0.38 (0.28 – 0.52)	< 0.001	0.43 (0.28 – 0.65)	< 0.001
Cold	0.42 (0.33 – 0.55)	< 0.001	0.40 (0.32 – 0.50)	< 0.001	0.70 (0.58 – 0.85)	< 0.001	0.65 (0.50 – 0.86)	0.002
Cough	0.33 (0.25 – 0.44)	< 0.001	0.37 (0.28 – 0.47)	< 0.001	0.62 (0.49 – 0.78)	< 0.001	0.55 (0.40 – 0.75)	< 0.001
Shortness of breath	0.22 (0.16 – 0.31)	< 0.001	0.28 (0.21 – 0.37)	< 0.001	0.33 (0.26 – 0.43)	< 0.001	0.37 (0.26 – 0.53)	< 0.001
Fatigue	0.20 (0.15 – 0.26)	< 0.001	0.33 (0.26 – 0.42)	< 0.001	0.42 (0.35 – 0.50)	< 0.001	0.45 (0.35 – 0.59)	< 0.001
Sleeping problems	0.23 (0.17 – 0.30)	< 0.001	0.28 (0.22 – 0.37)	< 0.001	0.36 (0.29 – 0.44)	< 0.001	0.37 (0.28 – 0.51)	< 0.001
Nausea	0.39 (0.30 – 0.52)	< 0.001	0.45 (0.35 – 0.58)	< 0.001	0.35 (0.29 – 0.43)	< 0.001	0.41 (0.31 – 0.54)	< 0.001
Vomiting	0.34 (0.18 – 0.63)	< 0.001	0.51 (0.27 – 0.97)	0.039	0.69 (0.39 – 1.21)	0.193	0.63 (0.29 – 1.37)	0.244
Diarrhoea	0.23 (0.16 – 0.32)	< 0.001	0.26 (0.19 – 0.35)	< 0.001	0.40 (0.30 – 0.53)	< 0.001	0.47 (0.31 – 0.72)	< 0.001
Abdominal pain	0.28 (0.21 – 0.36)	< 0.001	0.29 (0.23 – 0.37)	< 0.001	0.34 (0.28 – 0.41)	< 0.001	0.33 (0.25 – 0.43)	< 0.001
Headache	0.35 (0.27 – 0.45)	< 0.001	0.37 (0.30 – 0.46)	< 0.001	0.38 (0.32 – 0.45)	< 0.001	0.44 (0.34 – 0.57)	< 0.001
Dizziness	0.24 (0.18 – 0.31)	< 0.001	0.34 (0.27 – 0.43)	< 0.001	0.32 (0.26 – 0.39)	< 0.001	0.40 (0.30 – 0.52)	< 0.001
Fainting	0.32 (0.15 – 0.68)	0.003	0.50 (0.23 – 1.11)	0.088	0.38 (0.21 – 0.70)	0.002	0.19 (0.10 – 0.37)	< 0.001
Myalgia	0.50 (0.37 – 0.69)	< 0.001	0.44 (0.34 – 0.58)	< 0.001	0.30 (0.23 – 0.38)	< 0.001	0.63 (0.47 – 0.84)	0.002
Joint pain	0.24 (0.18 – 0.33)	< 0.001	0.37 (0.28 – 0.49)	< 0.001	0.35 (0.28 – 0.44)	< 0.001	0.41 (0.30 – 0.57)	< 0.001
Muscle contractions	0.22 (0.17 – 0.30)	< 0.001	0.37 (0.28 – 0.49)	< 0.001	0.34 (0.27 – 0.43)	< 0.001	0.47 (0.33 – 0.66)	< 0.001
Sweating			0.25 (0.18 – 0.34)	< 0.001	0.32 (0.24 – 0.43)	< 0.001	0.40 (0.26 – 0.62)	< 0.001
Rash	0.25 (0.18 – 0.34)	< 0.001			0.13 (0.10 – 0.16)	< 0.001	0.25 (0.18 – 0.35)	< 0.001
Itch	0.33 (0.24 – 0.45)	< 0.001	0.12 (0.10 – 0.16)	< 0.001			0.38 (0.28 – 0.53)	< 0.001
Other symptoms	0.40 (0.26 – 0.60)	< 0.001	0.25 (0.18 – 0.34)	< 0.001	0.39 (0.28 – 0.52)	< 0.001		

[1]reference category = presence of the adverse event.

Appendix 10 Survey on tolerability – Sickness at the time of or during the week before vaccination and underlying illness

Table A10.1 Proportions of reported sickness at the time of vaccination by birth cohort

Sickness at the time of vaccination	1st dose		2nd dose		3rd dose	
	All participants % (95% CI)	Complete responders % (95% CI)	All participants % (95% CI)	Complete responders % (95% CI)	All participants % (95% CI)	Complete responders % (95% CI)
Cold	10.9 (10.0 – 12.0)	11.5 (10.1 – 13.2)	12.3 (11.1 – 13.6)	12.8 (11.2 – 14.5)	18.4 (16.7 – 20.1)	18.3 (16.5 – 20.2)
1993	11.6 (9.8 – 13.7)	11.2 (8.5 – 14.5)	11.2 (9.1 – 13.7)	10.5 (7.9 – 13.8)	15.3 (12.5 – 18.6)	14.7 (11.6 – 18.4)
1994	10.1 (8.3 – 12.1)	10.7 (8.1 – 14.0)	14.8 (12.3 – 17.6)	15.8 (12.6 – 19.5)	18.6 (15.5 – 22.1)	17.5 (14.2 – 21.4)
1995	11.8 (9.9 – 14.1)	11.1 (8.2 – 14.8)	12.9 (10.4 – 15.8)	13.2 (10.1 – 17.1)	18.3 (15.1 – 22.0)	19.1 (15.4 – 23.5)
1996	10.6 (8.7 – 12.9)	13.5 (10.3 – 17.5)	10.1 (7.9 – 12.9)	11.7 (8.7 – 15.5)	21.4 (17.9 – 25.4)	22.3 (18.2 – 26.9)
Flu	0.8 (0.6 – 1.2)	0.7 (0.4 – 1.3)	0.7 (0.4 – 1.1)	0.6 (0.3 – 1.1)	1.1 (0.7 – 1.7)	0.9 (0.5 – 1.5)
1993	1.3 (0.7 – 2.2)	1.1 (0.4 – 2.7)	1.1 (0.5 – 2.2)	1.5 (0.7 – 3.3)	1.4 (0.7 – 2.9)	1.3 (0.5 – 3.0)
1994	0.7 (0.3 – 1.4)	0.7 (0.2 – 2.1)	1.0 (0.4 – 2.1)	0.4 (0.1 – 1.7)	1.1 (0.4 – 2.4)	0.9 (0.3 – 2.4)
1995	1.0 (0.5 – 1.9)	0.8 (0.2 – 2.4)	0.2 (0.0 – 1.0)	0.0 (0.0 – 1.2)	1.0 (0.4 – 2.4)	1.0 (0.3 – 2.8)
1996	0.3 (0.1 – 1.1)	0.3 (0.0 – 1.7)	0.3 (0.1 – 1.3)	0.3 (0.0 – 1.7)	1.0 (0.4 – 2.5)	0.3 (0.0 – 1.7)
Other	4.2 (3.6 – 4.9)	3.6 (2.8 – 4.6)	2.6 (2.1 – 3.3)	2.6 (1.9 – 3.5)	2.4 (1.8 – 3.2)	2.0 (1.4 – 2.8)
1993	3.6 (2.6 – 5.0)	3.1 (1.8 – 5.2)	2.6 (1.6 – 4.0)	2.9 (1.6 – 5.0)	2.7 (1.6 – 4.5)	2.0 (1.0 – 3.8)
1994	4.2 (3.1 – 5.7)	3.5 (2.1 – 5.7)	2.5 (1.5 – 4.0)	2.4 (1.3 – 4.4)	1.4 (0.7 – 2.9)	1.5 (0.7 – 3.3)
1995	4.9 (3.6 – 6.5)	3.9 (2.3 – 6.5)	2.4 (1.4 – 3.9)	2.1 (1.0 – 4.2)	2.8 (1.6 – 4.7)	2.6 (1.3 – 4.9)
1996	4.1 (2.9 – 5.7)	4.0 (2.3 – 6.6)	3.2 (2.0 – 5.0)	2.9 (1.5 – 5.3)	2.9 (1.6 – 4.9)	2.1 (1.0 – 4.3)

For numbers of participants for each dose and by birth cohort see chapter 5 - Table 9.
[1]$p < 0.05$ for trend in comparison of birth cohorts.

Table A10.2 Proportions of reported sickness during the week before vaccination by birth cohort

Sickness before vaccination	1st dose		2nd dose		3rd dose	
	All participants % (95% CI)	Complete responders % (95% CI)	All participants % (95% CI)	Complete responders % (95% CI)	All participants % (95% CI)	Complete responders % (95% CI)
Headache	13.6 (12.6 – 14.7) [1]	12.7 (11.1 – 14.4) [1]	11.3 (10.2 – 12.6) [1]	10.5 (9.1 – 12.1)	12.0 (10.7 – 13.5) [1]	11.5 (10.1 – 13.2)
1993	17.2 (15.1 – 19.7)	15.6 (12.4 – 19.3)	13.6 (11.3 – 16.3)	11.8 (9.1 – 15.3)	12.5 (9.9 – 15.6)	11.4 (8.7 – 14.8)
1994	15.6 (13.5 – 18.0)	16.0 (12.8 – 19.7)	11.9 (9.6 – 14.5)	11.4 (8.7 – 14.7)	14.7 (11.9 – 17.9)	13.1 (10.2 – 16.7)
1995	11.7 (9.8 – 14.0)	9.3 (6.7 – 12.8)	9.9 (7.7 – 12.5)	9.3 (6.7 – 12.8)	11.4 (8.8 – 14.6)	12.4 (9.4 – 16.2)
1996	8.8 (7.1 – 11.0)	8.8 (6.2 – 12.2)	9.7 (7.5 – 12.3)	9.3 (6.6 – 12.8)	9.2 (6.8 – 12.2)	9.0 (6.4 – 12.5)
Cold	13.2 (12.1 – 14.3)	14.2 (12.6 – 16.0)	12.1 (10.9 – 13.4)	12.8 (11.3 – 14.6)	20.1 (18.4 – 21.8)	20.2 (18.3 – 22.2)
1993	15.3 (13.2 – 17.6)	15.1 (12.0 – 18.8)	10.6 (8.6 – 13.1)	11.2 (8.5 – 14.5)	22.5 (19.1 – 26.2)	22.4 (18.7 – 26.5)
1994	12.2 (10.3 – 14.4)	13.1 (10.2 – 16.7)	14.2 (11.8 – 17.0)	14.4 (11.4 – 18.1)	19.5 (16.3 – 23.1)	19.0 (15.6 – 23.0)
1995	13.4 (11.3 – 15.8)	15.0 (11.7 – 19.0)	13.7 (11.1 – 16.6)	14.2 (11.0 – 18.2)	19.3 (16.0 – 23.1)	20.2 (16.3 – 24.6)
1996	11.9 (9.8 – 14.3)	13.8 (10.6 – 17.8)	9.8 (7.7 – 12.5)	11.7 (8.7 – 15.5)	18.6 (15.3 – 22.4)	18.6 (14.8 – 22.9)
Flu	2.3 (1.9 – 2.9)	2.5 (1.8 – 3.4)	1.4 (1.0 – 2.0)	1.3 (0.8 – 2.0)	3.2 (2.6 – 4.1)	3.0 (2.2 – 3.9)
1993	2.5 (1.7 – 3.7)	2.6 (1.4 – 4.7)	1.8 (1.0 – 3.1)	1.5 (0.7 – 3.3)	3.6 (2.2 – 5.5)	3.9 (2.4 – 6.3)
1994	2.5 (1.7 – 3.7)	2.8 (1.6 – 4.9)	1.4 (0.7 – 2.6)	1.1 (0.4 – 2.7)	3.0 (1.8 – 4.9)	2.2 (1.1 – 4.1)
1995	2.2 (1.4 – 3.5)	3.1 (1.7 – 5.5)	1.4 (0.7 – 2.8)	1.3 (0.5 – 3.2)	3.9 (2.5 – 6.1)	3.9 (2.3 – 6.5)
1996	2.1 (1.3 – 3.4)	1.3 (0.5 – 3.2)	1.1 (0.5 – 2.4)	1.3 (0.5 – 3.2)	2.4 (1.3 – 4.4)	1.9 (0.8 – 4.0)

For numbers of participants for each dose and by birth cohort see chapter 5 - Table 9.
[1] $p < 0.05$ for trend in comparison of birth cohorts.

Table A10.3 Proportions of reported underlying illness

Underlying illness*	1st dose % (95% CI)	2nd dose % (95% CI)	3rd dose % (95% CI)	Complete responders % (95% CI)
Total	33.5 (32.1 – 35.0)	33.0 (31.2 – 34.9)	33.1 (31.0 – 35.2)	33.5 (31.2 – 35.8)
1993	34.8 (32.0 – 37.8)	33.5 (30.0 – 37.1)	33.8 (29.8 – 38.0)	33.6 (29.3 – 38.1)
1994	31.9 (29.1 – 34.9)	32.9 (29.4 – 36.6)	32.4 (28.5 – 36.6)	34.1 (29.8 – 38.7)
1995	35.2 (32.2 – 38.4)	35.3 (31.4 – 39.3)	34.0 (29.7 – 38.5)	34.9 (30.2 – 39.9)
1996	31.5 (28.5 – 34.8)	29.9 (26.2 – 33.9)	31.7 (27.5 – 36.3)	30.8 (26.2 – 35.7)
Eczema	14.4 (13.3 – 15.5)	14.4 (13.0 – 15.8)	14.5 (13.0 – 16.1)	14.8 (13.1 – 16.6)
1993	15.9 (13.8 – 18.3)	14.3 (11.8 – 17.2)	15.6 (12.6 – 19.0)	14.5 (11.4 – 18.1)
1994	12.8 (10.9 – 15.1)	13.8 (11.3 – 16.6)	13.4 (10.7 – 16.6)	15.1 (12.0 – 18.8)
1995	14.7 (12.5 – 17.1)	15.9 (13.1 – 19.2)	14.1 (11.1 – 17.7)	15.2 (11.9 – 19.3)
1996	14.0 (11.8 – 16.5)	13.5 (10.9 – 16.7)	15.0 (11.9 – 18.7)	14.1 (10.8 – 18.1)
Allergy	12.8 (11.8 – 13.9) [1]	12.8 (11.6 – 14.2)	12.5 (11.1 – 14.0)	12.8 (11.3 – 14.6)
1993	14.8 (12.8 – 17.1)	14.0 (11.5 – 16.9)	13.7 (10.9 – 17.0)	13.6 (10.7 – 17.2)
1994	12.7 (10.7 – 14.9)	13.0 (10.6 – 15.8)	12.8 (10.1 – 16.0)	13.6 (10.6 – 17.1)
1995	13.7 (11.6 – 16.1)	14.2 (11.6 – 17.4)	12.8 (10.0 – 16.3)	13.7 (10.5 – 17.6)
1996	9.4 (7.6 – 11.6)	9.6 (7.4 – 12.4)	10.1 (7.6 – 13.4)	10.1 (7.3 – 13.7)
Asthma	8.9 (8.0 – 9.8)	8.3 (7.3 – 9.5)	8.2 (7.0 – 9.5)	8.1 (6.9 – 9.5)
1993	9.5 (7.8 – 11.4)	8.9 (7.0 – 11.4)	8.7 (6.5 – 11.6)	8.8 (6.4 – 11.8)
1994	7.4 (5.9 – 9.2)	6.9 (5.1 – 9.1)	6.8 (4.9 – 9.4)	7.0 (4.9 – 9.8)
1995	10.4 (8.6 – 12.6)	9.7 (7.5 – 12.4)	9.0 (6.6 – 12.0)	9.0 (6.5 – 12.5)
1996	8.0 (6.3 – 10.1)	7.7 (5.7 – 10.2)	8.1 (5.9 – 11.2)	7.4 (5.1 - 10.7)
Hay fever	8.1 (7.3 – 9.0) [1]	8.2 (7.2 – 9.3)	8.2 (7.0 – 9.5)	8.1 (6.9 – 9.6)
1993	9.4 (7.7 – 11.3)	9.4 (7.4 – 11.9)	9.5 (7.2 – 12.4)	9.0 (6.6 – 12.1)
1994	7.8 (6.2 – 9.6)	7.6 (5.8 – 10.0)	7.2 (5.2 – 9.8)	7.4 (5.3 – 10.3)
1995	9.1 (7.4 – 11.2)	9.5 (7.3 – 12.2)	10.7 (8.1 – 13.9)	10.9 (8.0 – 14.5)
1996	5.9 (4.5 – 7.8)	6.0 (4.3 – 8.4)	5.3 (3.5 – 7.9)	5.3 (3.4 – 8.2)
Diabetes mellitus	0.5 (0.3 – 0.8)	0.5 (0.3 – 0.9)	0.6 (0.3 – 1.0)	0.5 (0.3 – 1.1)
1993	0.6 (0.2 – 1.3)	0.4 (0.1 – 1.4)	0.8 (0.2 – 2.1)	0.7 (0.2 – 2.1)
1994	0.5 (0.2 – 1.2)	0.6 (0.2 – 1.6)	0.6 (0.1 – 1.8)	0.4 (0.1 – 1.7)
1995	0.7 (0.3 – 1.6)	0.8 (0.3 – 2.1)	0.6 (0.2 – 2.0)	0.8 (0.2 – 2.4)
1996	0.1 (0.0 – 0.8)	0.2 (0.0 – 1.1)	0.2 (0.0 – 1.4)	0.3 (0.0 – 1.7)

Table A10.3 continuing on the next page

Table A10.3 - Continued

Underlying illness*	1st dose % (95% CI)	2nd dose % (95% CI)	3rd dose % (95% CI)	Complete responders % (95% CI)
Other	5.6 (4.9 – 6.4)	5.2 (4.4 - 6.2)	5.1 (4.2 – 6.2)	5.3 (4.3 – 6.5)
1993	4.9 (3.7 – 6.4)	5.1 (3.6 – 7.0)	5.3 (3.6 – 7.7)	5.5 (3.7 – 8.1)
1994	5.3 (4.0 – 6.9)	5.1 (3.6 – 7.1)	4.5 (3.0 – 6.7)	4.8 (3.1 – 7.3)
1995	5.9 (4.5 – 7.6)	4.9 (3.4 – 7.1)	5.1 (3.4 – 7.6)	4.7 (2.9 – 7.4)
1996	6.8 (5.2 – 8.7)	5.9 (4.1 – 8.2)	5.7 (3.8 – 8.4)	6.4 (4.2 – 9.5)

For numbers of participants for each dose and by birth cohort see chapter 5 - Table 9.
*Information was only available if (also) the first questionnaire was returned; this information was not requested in the second and third questionnaire.
[1]$p < 0.05$ for trend in comparison of birth cohorts.

Table A10.4 Association between underlying illness, sickness during the week before or at the time of vaccination and AEs (corrected for dose and birth cohort)

Adverse event	Underlying illness*		Sickness at the time of vaccination		Sickness before vaccination	
	OR[1] (95% CI)	significance	OR[2] (95% CI)	significance	OR[3] (95% CI)	significance
Swelling	1.15 (0.99 – 1.34)	0.059	1.17 (1.00-1.38)	0.052	1.27 (1.10-1.46)	< 0.001
Redness	1.13 (0.98 – 1.31)	0.103	1.27 (1.08-1.49)	0.004	1.41 (1.22-1.62)	< 0.001
Pain	1.09 (0.95 – 1.25)	0.222	1.39 (1.79-1.63)	< 0.001	1.68 (1.46-1.94)	< 0.001
Swelling in the armpit	1.36 (0.93 – 1.98)	0.113	1.70 (1.14-2.54)	0.010	1.50 (1.04-2.18)	0.032
Reduced use of the arm	1.09 (0.97 – 1.23)	0.162	1.24 (1.09-1.42)	0.002	1.45 (1.29-1.64)	< 0.001
Fever (> 38 °C)	1.48 (1.16 – 1.89)	0.002	2.69 (2.10 – 3.44)	< 0.001	2.31 (1.82 – 2.92)	< 0.001
Listlessness	1.16 (1.00 – 1.35)	0.049	1.88 (1.60 – 2.20)	< 0.001	2.28 (1.99 – 2.62)	< 0.001
Crying	1.09 (0.85 – 1.40)	0.483	1.66 (1.28 – 2.16)	< 0.001	2.42 (1.93 – 3.04)	< 0.001
Cold	1.27 (1.12 – 1.45)	< 0.001	6.39 (5.59 – 7.29)	< 0.001	4.49 (3.98 – 5.07)	< 0.001
Cough	1.28 (1.09 – 1.51)	0.002	4.32 (3.69 – 5.06)	< 0.001	3.49 (3.00 – 4.06)	< 0.001
Shortness of breath	1.71 (1.40 – 2.10)	< 0.001	2.44 (1.99 – 3.01)	< 0.001	2.48 (2.05 – 3.01)	< 0.001
Fatigue	1.23 (1.08 – 1.40)	0.002	1.95 (1.69 – 2.24)	< 0.001	2.41 (2.13 – 2.72)	< 0.001
Sleeping problems	1.30 (1.10 – 1.53)	0.002	1.68 (1.41 – 2.01)	< 0.001	2.04 (1.74 – 2.38)	< 0.001
Nausea	1.27 (1.09 – 1.48)	0.002	1.53 (1.29 – 1.80)	< 0.001	2.22 (1.92 – 2.57)	< 0.001
Vomiting	1.35 (0.91 – 1.99)	0.134	1.38 (0.89 – 2.16)	0.150	1.67 (1.14 – 2.46)	0.009
Diarrhoea	1.10 (0.87 – 1.39)	0.404	1.43 (1.11 – 1.85)	0.006	1.71 (1.37 – 2.14)	< 0.001
Abdominal pain	1.16 (0.99 – 1.34)	0.059	1.54 (1.31 – 1.80)	< 0.001	2.14 (1.86 – 2.46)	< 0.001
Headache	1.29 (1.14 – 1.46)	< 0.001	1.70 (1.48 – 1.95)	< 0.001	3.68 (3.26 – 4.14)	< 0.001
Dizziness	1.29 (1.11 – 1.49)	< 0.001	1.67 (1.43 – 1.96)	< 0.001	2.37 (2.07 – 2.72)	< 0.001
Fainting	1.14 (0.69 – 1.90)	0.607	2.34 (1.40 – 3.92)	0.001	1.45 (0.87 – 2.40)	0.155
Myalgia	1.07 (0.95 – 1.22)	0.275	1.15 (1.00 – 1.32)	0.054	1.27 (1.12 – 1.43)	< 0.001
Joint pain	1.17 (0.98 – 1.40)	0.086	1.48 (1.21 – 1.80)	< 0.001	1.53 (1.28 – 1.82)	< 0.001
Muscle contractions	1.12 (0.93 – 1.34)	0.227	1.23 (1.00 – 1.51)	0.055	1.32 (1.10 – 1.58)	0.003
Sweating	1.20 (0.94 – 1.54)	0.150	1.37 (1.03 – 1.82)	0.031	1.62 (1.27 – 2.08)	< 0.001
Rash	1.56 (1.27 – 1.93)	< 0.001	1.64 (1.30 – 2.07)	< 0.001	1.65 (1.34 – 2.03)	< 0.001
Itch	1.43 (1.19 – 1.72)	< 0.001	1.10 (0.89 – 1.36)	0.373	1.32 (1.10 – 1.58)	0.003
Other symptoms	1.26 (0.99 – 1.60)	0.062	2.69 (2.10 – 3.44)	0.711	2.31 (1.82 – 2.92)	0.092

*Information was only available if (also) the first questionnaire was returned; this information was not requested in the second and third questionnaire.
[1]reference category = absence of underlying illness (eczema, allergy, asthma, hay fever, and diabetes mellitus).
[2]reference category = absence of sickness at the time of vaccination (cold or flu).
[3]reference category = absence of sickness during the week before vaccination (headache, cold or flu).

Appendix 11 Survey on tolerability – Absence and medical interventions

Table A11.1 Proportions of reported absence within seven days after immunisation by birth cohort

Absence after vaccination	1st dose				2nd dose				3rd dose			
	All participants		Complete responders		All participants		Complete responders		All participants		Complete responders	
	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days
Total	15.9 (14.8 – 17.1)		13.1 (11.5 – 14.8)		7.2 (6.2 – 8.2)		6.5 (5.4 – 7.9)		10.4 (9.2 – 11.8)		9.5 (8.2 – 11.0)	
1993	16.0 (13.9 – 18.4)		12.9 (10.1 – 16.5)		8.1 (6.3 – 10.3)		7.2 (5.1 – 10.1)		10.9 (8.5 – 13.8)		9.2 (6.8 – 12.3)	
1994	17.4 (15.1 – 19.8)		14.4 (11.4 – 18.1)		6.7 (5.0 – 8.8)		5.7 (3.8 – 8.3)		8.9 (6.8 – 11.7)		8.3 (6.0 – 11.3)	
1995	16.2 (13.9 – 18.7)		12.7 (9.6 – 16.5)		7.4 (5.5 – 9.8)		7.5 (5.2 – 10.7)		10.8 (8.3 – 13.9)		10.6 (7.8 -14.2)	
1996	13.7 (11.5 – 16.3)		11.9 (8.9 – 15.7)		6.4 (4.7 – 8.7)		5.8 (3.8 – 8.8)		11.0 (8.5 – 14.2)		10.1 (7.3 – 13.7)	
School	8.7 (7.9 – 9.7)	2.0	7.5 (6.3 – 8.9)	2.0	4.2 (3.5 – 5.0)	2.0	3.7 (2.9 – 4.7)	2.0	7.3 (6.2 – 8.5)	2.0	6.5 (5.4 – 7.9)	2.0
1993	8.6 (7.0 – 10.5)	2.0	5.9 (4.0 – 8.6)	2.0	4.4 (3.1 – 6.3)	2.0	3.3 (1.9 – 5.5)	2.0	7.1 (5.2 – 9.7)	2.0	5.7 (3.8 – 8.4)	2.5
1994	9.8 (8.1 – 11.8)	2.0	8.1 (5.8 – 11.1)	2.0	3.9 (2.7 – 5.7)	2.0	3.5 (2.1 – 5.7)	2.0	6.6 (4.8 – 9.1)	3.0	6.3 (4.4 – 9.1)	2.0
1995	8.8 (7.1 – 10.9)	3.0	8.3 (5.8 – 11.6)	2.5	4.9 (3.4 – 6.9)	3.0	5.2 (3.3 – 8.0)	2.5	7.5 (5.4 – 10.2)	2.5	7.0 (4.7 – 10.1)	2.0
1996	7.7 (6.0 – 9.7)	3.0	8.0 (5.5 – 11.3)	3.0	3.5 (2.3 – 5.4)	3.0	2.9 (1.5 – 5.3)	2.0	8.0 (5.8 – 10.8)	2.0	7.2 (4.9 – 10.4)	3.0
Sport	9.9 (9.0 – 10.8) [1, 2]	2.0	7.8 (6.6 – 9.2)	2.0	4.6 (3.8 – 5.5)	2.0	4.2 (3.3 – 5.3)	2.0	5.4 (4.5 – 6.4)	2.0	4.7 (3.8 – 5.9)	2.0
1993	9.5 (7.8 – 11.4)	2.0	8.3 (6.0 – 11.4)	2.0	4.6 (3.2 – 6.4)	2.0	4.6 (2.9 – 7.1)	2.0	4.6 (3.1 – 6.8)	3.0	4.2 (2.6 – 6.5)	4.0
1994	10.2 (8.4 – 12.2)	3.0	7.7 (5.5 – 10.6)	2.0	3.9 (2.7 – 5.7)	2.0	3.3 (1.9 – 5.5)	2.0	4.5 (3.0 – 6.6)	2.0	3.9 (2.4 – 6.3)	2.0
1995	10.3 (8.5 – 12.5)	3.0	7.5 (5.2 – 10.7)	2.0	5.0 (3.5 – 7.1)	2.0	4.7 (2.9 – 7.4)	3.0	6.5 (4.6 – 9.1)	2.0	5.9 (3.9 – 8.9)	2.0
1996	9.4 (7.6 – 11.6)	2.0	7.4 (5.1 – 10.7)	3.0	5.0 (3.5 – 7.1)	2.0	4.2 (2.5 – 6.9)	2.0	5.9 (4.1 – 8.5)	30	4.8 (2.9 – 7.6)	2.0
Other activities	2.9 (2.4 – 3.5)	3.0	2.0 (1.4 – 2.8) [1]	2.0	1.3 (0.9 – 1.8)	2.0	1.0 (0.6 – 1.6)	2.0	1.6 (1.1 – 2.3)	2.0	1.3 (0.8 – 2.0)	2.0
1993	3.6 (2.6 – 5.0)	3.0	2.2 (1.1 – 4.1)	3.0	1.9 (1.1 – 3.2)	2.0	1.1 (0.4 – 2.7)	2.0	2.1 (1.2 – 3.8)	2.0	2.0 (1.0 – 3.8)	2.0
1994	2.5 (1.7 – 3.7)	3.0	2.6 (1.4 – 4.7)	2.0	1.5 (0.8 – 2.8)	2.0	1.5 (0.7 – 3.3)	2.0	1.3 (0.5 – 2.7)	3.0	0.9 (0.3 – 2.4)	2.5
1995	3.6 (2.6 – 5.1)	2.0	2.6 (1.3 – 4.9)	2.0	1.3 (0.6 – 2.6)	3.0	0.8 (0.2 – 2.4)	2.0	2.0 (1.0 – 3.7)	2.0	1.6 (0.6 – 3.5)	2.0
1996	2.0 (1.2 – 3.2)	3.0	0.5 (0.1 – 2.1)	4.5	0.3 (0.1 – 1.3)	2.0	0.3 (0.0 – 1.7)	1.0	1.0 (0.4 – 2.5)	20	0.8 (0.2 – 2.5)	2.0

Table A11.1 continuing on the next page

Table A11.1 - Continued

Absence after vaccination	1st dose				2nd dose				3rd dose			
	All participants		Complete responders		All participants		Complete responders		All participants		Complete responders	
	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days
Parents or guardian from work	2.1 (1.7 – 2.6) [1]	2.0	1.5 (1.0 – 2.3) [1]	2.0	0.9 (0.6 – 1.3)	2.5	0.7 (0.4 – 1.3)	2.5	0.8 (0.5 – 1.3)	2.0	0.5 (0.3 – 1.1)	2.0
1993	1.2 (0.7 – 2.1)	2.0	0.7 (0.2 – 2.1)	1.0	0.8 (0.3 – 1.8)	2.0	0.4 (0.1 – 1.8)	1.5	0.9 (0.3 – 2.2)	2.0	0.7 (0.2 – 2.1)	3.0
1994	1.7 (1.1 – 2.8)	2.5	1.1 (0.4 – 2.7)	3.0	0.7 (0.3 – 1.7)	3.0	0.9 (0.3 – 2.4)	2.0	0.7 (0.2 – 2.0)	3.0	0.0 (0.0 – 1.0)	NA
1995	2.3 (1.5 – 3.6)	2.5	2.6 (1.3 – 4.9)	2.0	0.9 (0.4 – 2.1)	2.5	0.8 (0.2 – 2.4)	3.0	1.2 (0.5 – 2.7)	1.5	1.3 (0.5 – 3.2)	2.0
1996	3.5 (2.4 – 5.0)	3.0	2.1 (1.0 – 4.3)	2.0	1.1 (0.5 – 2.4)	3.0	0.8 (0.2 – 2.5)	3.0	0.4 (0.1 – 1.6)	2.0	0.3 (0.0 – 1.7)	2.0

NA = not applicable.
For numbers of participants for each dose and by birth cohort see chapter 5 - Table 9.
[1] $p < 0.05$ for trend in comparison of birth cohorts.

Table A11.2 Proportions of reported use of analgesics within seven days after immunisation by birth cohort

Analgesic	1st dose				2nd dose				3rd dose			
	All participants		Complete responders		All participants		Complete responders		All participants		Complete responders	
	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days
Total[3]	15.0 (13.9 – 16.1)	2.0	13.9 (12.3 – 15.6)	1.0	9.7 (8.6 – 10.8)	1.0	9.0 (7.7 – 10.5)	1.0	11.0 (9.7 – 12.4)	1.0	9.8 (8.4 – 11.3)	1.0
1993	15.7 (13.6 – 18.0)	2.0	14.3 (11.2 – 17.9)	1.0	10.2 (8.2 – 12.7)	2.0	9.2 (6.8 – 12.3)	2.0	10.5 (8.2 – 13.4)	1.0	9.6 (7.2 – 12.8)	1.0
1994	15.2 (13.1 – 17.6)	2.0	13.8 (10.8 – 17.4)	1.0	8.8 (6.9 – 11.2)	2.0	8.5 (6.2 – 11.6)	2.0	10.0 (7.7 – 12.9)	2.0	8.3 (6.0 – 11.3)	1.0
1995	15.1 (12.9 – 17.6)	2.0	14.7 (11.4 – 18.7)	1.0	10.8 (8.6 – 13.6)	2.0	11.6 (8.7 – 15.3)	1.0	12.8 (10.1 – 16.1)	2.0	12.9 (9.8 – 16.8)	1.5
1996	13.9 (11.6 – 16.4)	1.0	12.5 (9.4 – 16.3)	1.0	8.9 (6.8 – 11.4)	1.0	6.6 (4.4 – 9.8)	1.0	10.8 (8.3 – 14.0)	1.0	8.2 (5.7 – 11.6)	1.0
Paracetamol	14.1 (13.1 – 15.3)	2.0	13.1 (11.5 – 14.8)	1.0	9.2 (8.2 – 10.4)	1.0	8.6 (7.3 – 10.1)	1.0	10.0 (8.8 – 11.4)	1.0	8.9 (7.6 – 10.4)	1.0
1993	14.3 (12.3 – 16.5)	2.0	13.2 (10.3 – 16.7)	1.0	9.3 (7.4 – 11.7)	2.0	8.8 (6.4 – 11.8)	2.0	9.6 (7.4 – 12.4)	1.0	8.8 (6.4 – 11.8)	1.0
1994	14.7 (12.6 – 17.0)	2.0	13.6 (10.6 – 17.1)	1.0	8.8 (6.9 – 11.2)	2.0	8.5 (6.2 – 11.6)	2.0	9.1 (6.9 – 11.9)	2.0	7.7 (5.5 – 10.6)	1.0
1995	14.5 (12.3 – 16.9)	2.0	14.0 (10.7 – 17.9)	1.0	10.5 (8.3 – 13.2)	2.0	11.1 (8.2 – 14.8)	1.0	11.6 (9.0 – 14.8)	2.0	11.9 (8.9 – 15.6)	1.0
1996	13.3 (11.1 – 15.8)	1.0	11.4 (8.5 – 15.2)	1.0	8.4 (6.4 – 10.9)	1.0	6.1 (4.0 – 9.1)	1.0	10.0 (7.6 – 13.1)	1.0	7.7 (5.3 – 11.0)	1.0

Table A11.2 continuing on the next page

Table A11.2 - Continued

Analgesic	1st dose				2nd dose				3rd dose			
	All participants		Complete responders		All participants		Complete responders		All participants		Complete responders	
	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days	% (95% CI)	Median duration in days
Nerofen	0.3 (0.1 – 0.5)	3.0	0.2 (0.0 – 0.6)	5.0	0.1 (0.0 – 0.4)	4.0	0.1 (0.0 – 0.4)	5.0	0.2 (0.1 – 0.6)	3.0	0.2 (0.1 – 0.7)	2.5
1993	0.4 (0.1 – 1.0)	1.5	0.4 (0.1 – 1.8)	4.0	0.1 (0.0 – 0.9)	5.0	0.2 (0.0 – 1.4)	5.0	0.5 (0.1 – 1.7)	1.0	0.7 (0.2 – 2.1)	1.0
1994	0.3 (0.1 – 0.9)	3.0	0.0 (0.0 – 1.0)	NA	0.0 (0.0 – 0.7)	NA	0.0 (0.0 – 1.0)	NA	0.0 (0.0 – 0.9)	NA	0.0 (0.0 – 1.0)	NA
1995	0.3 (0.1 – 1.0)	4.0	0.3 (0.0 – 1.7)	5.0	0.3 (0.1 – 1.3)	5.0	0.0 (0.0 – 1.2)	NA	0.2 (0.0 – 1.3)	4.0	0.3 (0.0 – 1.7)	4.0
1996	0.0 (0.0 – 0.6)	NA	0.0 (0.0 – 1.3)	NA	0.2 (0.0 – 1.0)	1.0	0.0 (0.0 – 1.3)	NA	0.2 (0.0 – 1.3)	3.0	0.0 (0.0 – 1.3)	NA
Homeopathic	0.2 (0.1 – 0.3)	5.0	0.1 (0.0 – 0.4)	5.0	0.2 (0.1 – 0.5)	3.5	0.1 (0.0 – 0.5)	1.5	0.2 (0.1 – 0.5)	2.5	0.1 (0.0 – 0.5)	3.5
1993	0.2 (0.0 – 0.7)	4.0	0.2 (0.0 – 1.4)	5.0	0.3 (0.0 – 1.1)	4.5	0.0 (0.0 – 1.0)	NA	0.2 (0.0 – 1.1)	6.0	0.2 (0.0 – 1.4)	6.0
1994	0.2 (0.0 – 0.8)	3.5	0.0 (0.0 – 1.0)	NA	0.0 (0.0 – 0.7)	NA	0.0 (0.0 – 1.0)	NA	0.0 (0.0 – 0.9)	NA	0.0 (0.0 – 1.0)	NA
1995	0.1 (0.0 – 0.7)	5.0	0.0 (0.0 – 1.2)	NA	0.5 (0.1 – 1.5)	2.0	0.5 (0.1 – 2.1)	1.5	0.2 (0.0 – 1.3)	2.0	0.0 (0.0 – 1.2)	NA
1996	0.1 (0.0 – 0.8)	5.0	0.0 (0.0 – 1.3)	NA	0.2 (0.0 – 1.0)	5.0	0.0 (0.0 – 1.3)	NA	0.4 (0.1 – 1.6)	2.0	0.3 (0.0 – 1.7)	1.0
Viburcol	0.0 (0.0 – 0.2)	1.0	0.0 (0.0 – 0.3)	NA	0.0 (0.0 – 0.2)	7.0	0.0 (0.0 – 0.3)	NA	0.0 (0.0 – 0.3)	2.0	0.1 (0.0 – 0.4)	2.0
1993	0.0 (0.0 – 0.4)	NA	0.0 (0.0 – 1.0)	NA	0.0 (0.0 – 0.6)	NA	0.0 (0.0 – 1.0)	NA	0.0 (0.0 – 0.8)	NA	0.0 (0.0 – 1.0)	NA
1994	0.1 (0.0 – 0.6)	1.0	0.0 (0.0 – 1.0)	NA	0.0 (0.0 – 0.7)	NA	0.0 (0.0 – 1.0)	NA	0.0 (0.0 – 0.9)	NA	0.0 (0.0 – 1.0)	NA
1995	0.0 (0.0 – 0.5)	NA	0.0 (0.0 – 1.2)	NA	0.2 (0.0 – 1.0)	7.0	0.0 (0.0 – 1.2)	NA	0.2 (0.0 – 1.3)	2.0	0.3 (0.0 – 1.7)	2.0
1996	0.0 (0.0 – 0.6)	NA	0.0 (0.0 – 1.3)	NA	0.0 (0.0 – 0.8)	NA	0.0 (0.0 – 1.3)	NA	0.0 (0.0 – 1.0)	NA	0.0 (0.0 – 1.3)	NA
Other	1.8 (1.4 – 2.3) [1]	2.0	1.4 (0.9 – 2.2)	2.0	1.2 (0.8 – 1.7) [1]	2.0	1.0 (0.6 – 1.6)	2.0	1.8 (1.3 – 2.5)	2.0	1.4 (0.9 – 2.1)	2.0
1993	2.7 (1.8 – 3.9)	2.0	1.1 (0.4 – 2.7)	3.0	2.2 (1.3 – 3.6)	2.0	1.1 (0.4 – 2.7)	4.0	1.6 (0.8 – 3.1)	2.0	1.1 (0.4 – 2.7)	3.0
1994	2.0 (1.3 – 3.1)	2.0	1.5 (0.7 – 3.3)	2.0	0.8 (0.3 – 1.9)	3.5	0.9 (0.3 – 2.4)	2.5	1.6 (0.8 – 3.1)	1.0	1.1 (0.4 – 2.7)	1.0
1995	1.2 (0.6 – 2.2)	1.0	1.6 (0.6 – 3.5)	1.0	1.1 (0.5 – 2.4)	2.0	1.0 (0.3 – 2.8)	2.0	2.6 (1.4 – 4.5)	2.0	2.3 (1.1 – 4.5)	2.0
1996	1.3 (0.7 – 2.4)	2.0	1.6 (0.6 – 3.6)	2.0	0.5 (0.1 – 1.5)	2.0	0.8 (0.2 – 2.5)	2.0	1.2 (0.5 – 2.8)	2.0	0.8 (0.2 – 2.5)	2.0

NA = not applicable.

For numbers of participants for each dose and by birth cohort see chapter 5 - Table 9.

[1] $p < 0.05$ for trend in comparison of birth cohorts.

[2] $p < 0.05$ for comparison of doses.

Table A11.3 Proportions of reported medical interventions by birth cohort

Medical intervention	1st dose		2nd dose		3rd dose	
	All participants % (95% CI)	Complete responders % (95% CI)	All participants % (95% CI)	Complete responders % (95% CI)	All participants % (95% CI)	Complete responders % (95% CI)
Total	1.5 (1.1 – 1.9) [1]	1.2 (0.7 – 1.9)	0.9 (0.6 – 1.4) [1]	1.1 (0.7 – 1.7) [1]	1.1 (0.7 – 1.6)	0.9 (0.5 – 1.5)
1993	2.2 (1.5 – 3.3)	1.5 (0.7 – 3.3)	0.5 (0.2 – 1.5)	0.4 (0.1 – 1.8)	2.0 (1.0 – 3.6)	1.3 (0.5 – 3.0)
1994	1.6 (1.0 – 2.7)	1.5 (0.7 – 3.3)	0.7 (0.3 – 1.7)	1.1 (0.4 – 2.7)	0.4 (0.1 – 1.4)	0.4 (0.1 – 1.7)
1995	0.5 (0.2 – 1.3)	0.0 (0.0 – 1.2)	0.8 (0.3 – 1.9)	0.2 (0.8 – 2.4)	1.2 (0.5 – 2.7)	1.0 (0.3 – 2.8)
1996	1.5 (0.8 – 2.6)	1.6 (0.6 – 3.6)	1.8 (0.9 – 3.2)	2.1 (1.0 – 4.3)	0.6 (0.2 – 1.9)	0.5 (0.1 – 2.1)
Visited a GP	0.9 (0.6 – 1.3)	0.8 (0.4 – 1.4)	0.5 (0.3 – 0.9)	0.5 (0.2 – 1.0)	0.7 (0.4 – 1.1)	0.5 (0.3 – 1.1)
1993	1.4 (0.8 – 2.3)	0.9 (0.3 – 2.4)	0.4 (0.1 – 1.3)	0.2 (0.0 – 1.4)	0.7 (0.2 – 1.9)	0.2 (0.0 – 1.4)
1994	1.1 (0.6 – 1.9)	0.9 (0.3 – 2.4)	0.4 (0.1 – 1.3)	0.7 (0.2 – 2.1)	0.4 (0.1 – 1.4)	0.4 (0.1 – 1.7)
1995	0.2 (0.0 – 0.9)	0.0 (0.0 – 1.2)	0.3 (0.1 – 1.3)	0.3 (0.0 – 1.7)	1.0 (0.4 – 2.4)	0.8 (0.2 – 2.4)
1996	0.9 (0.4 – 1.9)	1.3 (0.5 – 3.2)	1.0 (0.4 – 2.2)	0.8 (0.2 – 2.5)	0.4 (0.1 – 1.6)	0.5 (0.1 – 2.1)
Consulted GP by phone	0.6 (0.4 – 0.9)	0.4 (0.2 – 0.9)	0.4 (0.2 – 0.7)	0.4 (0.2 – 0.9)	0.5 (0.3 – 1.0)	0.3 (0.1 – 0.7)
1993	0.8 (0.4 – 1.6)	0.4 (0.1 – 1.8)	0.1 (0.0 – 0.9)	0.2 (0.0 – 1.4)	0.9 (0.3 – 2.2)	0.4 (0.1 – 1.8)
1994	0.8 (0.4 – 1.6)	0.1 (0.1 – 1.7)	0.3 (0.0 – 1.1)	0.4 (0.1 – 1.7)	0.2 (0.0 – 1.2)	0.2 (0.0 – 1.4)
1995	0.1 (0.0 – 0.7)	0.0 (0.0 – 1.2)	0.5 (0.1 – 1.5)	0.3 (0.0 – 1.7)	0.8 (0.3 – 2.1)	0.5 (0.1 – 2.1)
1996	0.8 (0.4 – 1.9)	0.8 (0.2 – 2.5)	0.6 (0.2 – 1.8)	0.8 (0.2 – 2.5)	0.2 (0.0 – 1.3)	0.0 (0.0 – 1.3)
Consulted MHS by phone	0.1 (0.0 – 0.3) [1]	0.2 (0.0 – 0.6)	0.1 (0.0 – 0.3)	0.1 (0.0 – 0.4)	0.0 (0.0 – 0.3)	0.1 (0.0 – 0.4)
1993	0.0 (0.0 – 0.4)	0.0 (0.0 – 1.0)	0.0 (0.0 – 0.6)	0.0 (0.0 – 1.0)	0.2 (0.0 – 1.1)	0.2 (0.0 – 1.4)
1994	0.1 (0.0 – 0.6)	0.2 (0.0 – 1.4)	0.0 (0.0 – 0.7)	0.0 (0.0 – 1.0)	0.0 (0.0 – 0.9)	0.0 (0.0 – 1.0)
1995	0.1 (0.0 – 0.7)	0.0 (0.0 – 1.2)	0.2 (0.0 – 1.0)	0.0 (0.0 – 1.2)	0.0 (0.0 – 0.9)	0.0 (0.0 – 1.2)
1996	0.3 (0.1 – 1.1)	0.5 (0.1 – 2.1)	1.8 (0.9 – 3.2)	0.3 (0.0 – 1.7)	0.0 (0.0 – 1.0)	0.0 (0.0 – 1.3)
Visited emergency room	0.0 (0.0 – 0.2)	0.0 (0.0 – 0.3)	0.0 (0.0 – 0.3)	0.1 (0.0 – 0.4)	0.1 (0.0 – 0.4)	0.1 (0.0 – 0.5)
1993	0.0 (0.0 – 0.4)	0.0 (0.0 – 1.0)	0.1 (0.0 – 0.9)	0.2 (0.0 – 1.4)	0.4 (0.1 – 1.4)	0.4 (0.1 – 1.8)
1994	0.1 (0.0 – 0.6)	0.0 (0.0 – 1.0)	0.0 (0.0 – 0.7)	0.0 (0.0 – 1.0)	0.0 (0.0 – 0.9)	0.0 (0.0 – 1.0)
1995	0.0 (0.0 – 0.5)	0.0 (0.0 – 1.2)	0.0 (0.0 – 0.7)	0.0 (0.0 – 1.2)	0.0 (0.0 – 0.9)	0.0 (0.0 – 1.2)
1996	0.0 (0.0 – 0.6)	0.0 (0.0 – 1.3)	0.0 (0.0 – 0.8)	0.0 (0.0 – 1.3)	0.0 (0.0 – 1.0)	0.0 (0.0 – 1.3)
Visited medical specialist	0.0 (0.0 – 0.1)	0.0 (0.0 – 0.3)	0.1 (0.0 – 0.3)	0.0 (0.0 – 0.3)	0.0 (0.0 – 0.2)	0.0 (0.0 – 0.3)
1993	0.0 (0.0 – 0.4)	0.0 (0.0 – 1.0)	0.3 (0.0 – 1.1)	0.0 (0.0 – 1.0)	0.0 (0.0 – 0.8)	0.0 (0.0 – 1.0)
1994	0.0 (0.0 – 0.5)	0.0 (0.0 – 1.0)	0.0 (0.0 – 0.7)	0.0 (0.0 – 1.0)	0.0 (0.0 – 0.9)	0.0 (0.0 – 1.0)
1995	0.0 (0.0 – 0.5)	0.0 (0.0 – 1.2)	0.0 (0.0 – 0.7)	0.0 (0.0 – 1.2)	0.0 (0.0 – 0.9)	0.0 (0.0 – 1.2)
1996	0.0 (0.0 – 0.6)	0.0 (0.0 – 1.3)	0.0 (0.0 – 0.8)	0.0 (0.0 – 1.3)	0.0 (0.0 – 1.0)	0.0 (0.0 – 1.3)

Table A11.3 continuing on the next page

Table A11.3 – Continued

Medical intervention	1st dose		2nd dose		3rd dose	
	All participants % (95% CI)	Complete responders % (95% CI)	All participants % (95% CI)	Complete responders % (95% CI)	All participants % (95% CI)	Complete responders % (95% CI)
Hospitalisation	0.0 (0.0 – 0.1)	0.0 (0.0 – 0.3)	0.0 (0.0 – 0.2)	0.0 (0.0 – 0.3)	0.0 (0.0 – 0.2)	0.0 (0.0 – 0.3)
1993	0.0 (0.0 – 0.4)	0.0 (0.0 – 1.0)	0.0 (0.0 – 0.6)	0.0 (0.0 – 1.0)	0.0 (0.0 – 0.8)	0.0 (0.0 – 1.0)
1994	0.0 (0.0 – 0.5)	0.0 (0.0 – 1.0)	0.0 (0.0 – 0.7)	0.0 (0.0 – 1.0)	0.0 (0.0 – 0.9)	0.0 (0.0 – 1.0)
1995	0.0 (0.0 – 0.5)	0.0 (0.0 – 1.2)	0.0 (0.0 – 0.7)	0.0 (0.0 – 1.2)	0.0 (0.0 – 0.9)	0.0 (0.0 – 1.2)
1996	0.0 (0.0 – 0.6)	0.0 (0.0 – 1.3)	0.0 (0.0 – 0.8)	0.0 (0.0 – 1.3)	0.0 (0.0 – 1.0)	0.0 (0.0 – 1.3)
Other	0.2 (0.1 – 0.4)	0.1 (0.0 – 0.4)	0.3 (0.1 – 0.6)	0.1 (0.0 – 0.7)	0.2 (0.1 – 0.5)	0.1 (0.0 – 0.5)
1993	0.3 (0.1 – 0.9)	0.2 (0.0 – 1.4)	0.1 (0.0 – 0.9)	0.2 (0.0 – 1.4)	0.7 (0.2 – 1.9)	0.4 (0.1 – 1.8)
1994	0.1 (0.0 – 0.6)	0.0 (0.0 – 1.0)	0.0 (0.0 – 0.7)	0.0 (0.0 – 1.0)	0.0 (0.0 – 0.9)	0.0 (0.0 – 1.0)
1995	0.0 (0.0 – 0.7)	0.0 (0.0 – 1.2)	0.5 (0.1 – 1.5)	0.5 (0.1 – 2.1)	0.0 (0.0 – 0.9)	0.0 (0.0 – 1.2)
1996	0.2 (0.0 – 0.9)	0.0 (0.0 – 1.3)	0.5 (0.1 – 1.5)	0.5 (0.1 – 2.1)	0.0 (0.0 – 1.0)	0.0 (0.0 – 1.3)

For numbers of participants for each dose and by birth cohort see chapter 5 - Table 9.
[1]$p < 0.05$ for trend in comparison of birth cohorts.
[2]$p < 0.05$ for comparison of doses.

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