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Sundheds- og ældreministeren

Dato: 4. december 2015
Enhed: Psykiatri og Lægemiddelpolitik
Sagsnr.: 1506455
Dok. nr.: 1827652

Nordisk Råds medlem Jan-Erik Messmann (DF) har stillet følgende spørgsmål til Nordisk Ministerråd:

"De nordiske ministre bedes redegøre for, hvordan man i deres respektive lande registrerer bivirkninger til HPV vaccine, samt hvor mange bivirkninger der er registreret? Har man i de respektive lande set en stigning i antallet af tilfælde, hvor man har registreret piger/kvinder med svimmelhed, besvimelse eller ledsmerter samt trætheds-syndrom?

Har man i de respektive lande set en øgning af ME-trætheds-syndrom, POTS eller andre tilsvarende sygdomme?"

./. Den danske lægemiddelstyrelse har til brug for besvarelsen af spørgsmålet indhentet bidrag fra Finland, Island, Norge og Sverige. Nedenfor fremgår et uddrag af de enkelte landes bidrag til besvarelsen. De fulde bidrag er vedlagt som bilag.

Danmark:
Lægemiddelstyrelsen har oplyst følgende, hvortil jeg kan henholde mig:

"Lægemiddelstyrelsen registrerer indberetninger om formodede bivirkninger ved HPV-vacciner i styrelsens bivirkningsdatabase. Ved registreringen anvender Lægemiddelstyrelsen samme kodningssystem som myndighederne i de andre EU-lande.

Læger, tandlæger, dyrlæger og jordemødre har pligt til at indberette formodede bivirkninger ved lægemidler i henhold til § 4 i bekendtgørelse om indberetning af bivirkninger ved lægemidler m.m. Efter 2 år fra markedsføringen af lægemidlet omfatter indberetningspligten dog alene alvorlige eller uventede bivirkninger. Andre sundhedspersoner og borgere har mulighed for at indberette formodede bivirkninger.

Indberetninger om formodede alvorlige bivirkninger ved HPV-vacciner sendes til den fælles europæiske bivirkningsdatabase (EudraVigilance-databasen). Alle formodede bivirkninger sendes til WHOs bivirkningsdatabase (Vigibase) og til den lægemiddelvirksomhed, der er indehaver af markedsføringstilladelsen.

Lægemiddelstyrelsen har pr. 28. oktober 2015 registreret 1916 indberetninger om formodede bivirkninger ved HPV-vacciner.

Opgjort på baggrund af modtagelsestidspunkt, er antallet af indberetninger med de nævnte symptomer (svimmelhed, besvimelse, ledsmerter og træthed) steget fra 2013 og fremefter."

Herudover oplyser styrelsen, at en opgørelse over de modtagne bivirkningsindberetninger i perioden 2009 til og med 30. juni 2015, opgjort på baggrund af tidspunktet

for bivirkningsstart, viser, at der er modtaget flest indberetninger med bivirkningsstart i 2013, dernæst i 2012 og 2009. Det er de år, hvor der er solgt flest doser af HPV-vacciner.

Lægemiddelstyrelsen oplyser videre, at når der ses på befolkningen generelt, er POTS og ME-træthedssyndrom begge sjældne diagnoser. Antallet af registrerede tilfælde i Landspatientregistret i perioden 2005-2014 viser, at der har været en stigning i antallet personer, der er registret med diagnosen POTS. Stigningen er mest markant for årene 2012-2014. For ME-træthedssyndrom har der været et fald i antallet af diagnosticerede tilfælde i årene 2005-2007 og en stigning i årene 2013-2014. Der henvises til tabellen i bidraget fra Danmark. Fordi der er tale om sjældne diagnoser, kan en ændring i registreringspraksis blandt sundhedspersonale forårsage store udslag i antal årligt registrerede tilfælde.

Der spørges endelig til forekomst af andre tilsvarende sygdomme. Herom oplyser Lægemiddelstyrelsen, at diagnosen Fibromyalgi registeres i Landspatientregistreret i Danmark med langt større hyppighed end ME-træthedssyndrom og POTS. Antallet af registrerede tilfælde i Landspatientregistret i perioden 2008-2014 viser, at antallet af fibromyalgidiagnoser var stigende indtil 2011, hvor det højeste antal blev diagnosticeret. Herefter har antallet været faldende. Der henvises til figur 1 og 2 i bidraget fra Danmark.

De øvrige nordiske lande oplyser til brug for besvarelsen af spørgsmålene følgende, som jeg kan henvise til:

"Finland:
Indberetninger om formodede bivirkninger registreres i Fimeas (Finnish Medicines Agency) bivirkningsdatabase, hvortil både sundhedspersoner og forbrugere kan indberette formodede bivirkninger ved lægemidler eller vacciner.

Sundhedspersoner har ifølge lovgivningen pligt til at indberette formodede bivirkninger ved vacciner.

Pr. 26. oktober 2015 var der registreret 205 indberetninger om formodede bivirkninger ved HPV-vacciner.

Der er modtaget 6 indberetninger om formodede bivirkninger, som beskriver kronisk træthedssyndrom, POTS, diverse neurologiske symptomer eller trætheds-symptomer. Disse indberetninger er alle modtaget efter februar 2015.

Der er foretaget en sammenligning mellem antallet af registrerede tilfælde af PANS, POTS og CFS/ME/SEID i Hospital Discharge Register (HILMO) i perioderne 2000-2009 og 2010-2013 blandt gruppen under 18 år. Der er ikke fundet indikation for en stigning i antallet af tilfælde med PANS, POTS eller CFS/ME/SEID.

Island:
Indberetninger om formodede bivirkninger skal indberettes til IMA (Icelandic Medicines Agency). Indberetninger om formodede bivirkninger ved HPV-vaccine håndteres på samme måde som indberetninger om formodede bivirkninger ved andre lægemidler.

Der er i perioden 2011 til nu modtaget ialt 10 indberetninger om formodede bivirkninger ved HPV-vaccinen Cervarix.

IMA har ikke adgang til information om, hvorvidt der er en stigning i antallet af tilfælde med piger/kvinder med svimmelhed, besvimelse, ledsmerter eller træthedssyndrom på Island. Endvidere har IMA på nuværende tidspunkt ikke data til rådighed, som gør det muligt at konkludere, om der har været en stigning i antallet af tilfælde af ME-træthedssyndrom, POTS eller andre tilsvarende sygdomme.

Norge:
Sundhedspersoner sender indberetninger om formodede bivirkninger til Folkehelseinstituttet (FHI).
Indberetningen registreres i den norske bivirkningsdatabase, som kommunikerer med andre internationale databaser, som den europæiske bivirkningsdatabase (EudraVigilance). Patienter kan indberette formodede bivirkninger anonymt direkte til Lægemiddelverket.

Indberetninger om formodede alvorlige bivirkninger videresendes til EudraVigilance og indehaveren af markedsføringstilladelsen.

Der er pr. 28. oktober 2015 registreret i alt 620 indberetninger om formodede bivirkninger ved HPV-vaccinen Gardasil.

Der er ikke foretaget populationsstudier, hvor man sammenligner forekomsten af de nævnte symptomer (svimmelhed, besvimelser, ledsmerter eller træthedssyndrom) blandt HPV-vaccinerede og ikke-vaccinerede. Man kan derfor ikke sige, om der er en ændring i forekomsten. Derimod er der foretaget et registerstudie for at kortlægge forekomsten af ME/CFS efter alder og køn i Norge 2008-2012. Der fandt man, at kvinder har en højere risiko for at få ME/CFS end mænd, og at symptomdebut ses hyppigere i enkelte aldersklasser.

Der gøres opmærksom på, at indberetninger om bivirkninger i et indberetningssystem som dette, ikke kan bruges som grundlag for at se på ændringer i frekvens, som man kan i kliniske studier. Der er mange faktorer og tilfældigheder som påvirker, hvorvidt en bivirkningsindberetning bliver indsendt eller ej. Bivirkningsindberetninger/spontanrapporter giver imidlertid værdifuld information om eventuelle nye bivirkninger, som opstår. Det er også vigtigt at være klar over, at en årsagssammenhæng ikke er etableret på indberetningstidspunktet, eftersom en bivirkningsindberetning sendes ind på mistanke om en sammenhæng mellem lægemidlet og det opståede symptom/sygdom.

Symptomerne svimmelhed og besvimelse bliver indberettet for flere typer af vacciner, og det skyldes som ofte en vasovagal reaktion, som blandt andet udløses ved skræmmende eller ubehagelige sanseindtryk (for eksempel injektionsproceduren). Typiske vasovagale symptomer er svimmelhed, bleghed, kvalme, lav puls, kortvarig blodtryksfald og i nogle tilfælde besvimelse. Ved en tolkning af data i bivirkningsindberetninger er det vigtigt, at man også ser på varigheden af symptomerne.

Sverige:
Läkemedelsverkets enhed for lægemiddelsikkerhed registrerer og håndterer modtagne indberetninger om formodede bivirkninger ens, uanset hvilket lægemiddel indberetningen omhandler. Der modtages indberetninger fra sundhedspersoner og fra forbrugere/patienter. Alle rapporter om formodede alvorlige bivirkninger sendes fra det svenske system videre til EudraVigilance.

Pr. 27. oktober 2015 har Sverige registreret 800 rapporter om formodede bivirkninger ved Gardasil og 3 rapporter om formodede bivirkninger ved Cervarix.

Der er modtaget i alt 5 rapporter om POTS. En rapport er modtaget i 2013, og fire rapporter er modtaget fra sommeren 2015. For de øvrige symptomer (svimmelhed, besvimelse, træthed) er det største antal rapporter modtaget i løbet af 2012. Dette ser også ud til at være tilfælde for artralgi (ledsmerter)."

Med venlig hilsen

Sophie Løhde

Besvarelse af skriftligt spørgsmål E 9/2015 fra Nordisk Råd om bivirkninger efter HPV-vaccination

Bidrag fra Danmark

De nordiske ministre bedes redegøre for, hvordan man i deres respektive lande registrerer bivirkninger til HPV vaccinen, samt hvor mange bivirkninger der er registreret?

I Danmark registrerer Lægemiddelstyrelsen alle indberetninger om formodede bivirkninger ved HPV-vacciner i styrelsens bivirkningsdatabase. For at standardisere indberetninger om formodede bivirkninger og derved kunne analysere på disse, anvender Lægemiddelstyrelsen og myndighederne i de andre EU-lande samme kodningssystem[1].

Læger, tandlæger, dyrlæger og jordemødre har pligt til at indberette formodede bivirkninger ved lægemidler i henhold til § 4 i bekendtgørelse om indberetning af bivirkninger ved lægemidler m.m[2]. Efter 2 år fra markedsføringen af lægemidlet omfatter indberetningspligten dog alene alvorlige eller uventede bivirkninger. Andre sundhedspersoner og borgere har mulighed for at indberette formodede bivirkninger.

Lægemiddelstyrelsen sender indberetninger om formodede alvorlige[3] bivirkninger ved HPV-vacciner til den fælles europæiske bivirkningsdatabase (EudraVigilance-databasen) hos Det Europæiske Lægemiddelagentur (EMA). Alle formodede bivirkninger sendes til WHOs bivirkningsdatabase (Vigibase) og til den lægemiddelvirksomhed, der er indehaver markedsføringstilladelsen[4].

I forbindelse med registreringen kontakter Lægemiddelstyrelsen ved uklarheder eller manglende oplysninger indberetter eller læge for en afklaring. Ved en indberetning modtaget fra en patient eller pårørende om formodede bivirkninger, som vurderes at være alvorlig, kontakter Lægemiddelstyrelsen rutinemæssigt patientens behandlende læge for at få bivirkningen medicinsk bekræftet. Det betyder, at lægen bliver spurgt om, hvorvidt patienten har oplevet den indberettede bivirkning, og om bivirkningen vurderes at have en sammenhæng med medicinen. Lægens svar registreres på sagen.

Lægemiddelstyrelsen har pr. 28. oktober 2015 registreret 1916 indberetninger om formodede bivirkninger ved HPV-vacciner.

Har man i de respektive lande set en stigning i antallet af tilfælde, hvor man har registreret piger/kvinder med svimmelhed, besvimelse eller ledsmerter samt træthedssyndrom?

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[1] Kodning i Medical Dictionary for Regulatory Activities terminology (MedDRA).

[2] Bekendtgørelse nr. 381 af 9. april 2014 om indberetning af bivirkninger ved lægemidler m.m.

[3] Ved en alvorlig bivirkning fremkaldt af et lægemiddel til mennesker forstås en bivirkning, som er dødelig, livstruende, kræver hospitalsindlæggelse eller forlængelse af hidtidig hospitalsindlæggelse, eller som resulterer i vedvarende eller betydelig invaliditet eller uarbejdsdygtighed, eller som er en medfødt anomali eller fødselsskade, jf. § 3, stk. 4, i bekendtgørelse nr. 391 af 9. april 2014 om indberetning af bivirkninger ved lægemidler m.m.

[4] De lægemiddelvirksomheder, som er indehavere af markedsføringstilladelser til HPV-vaccinerne, har pligt til at videresende oplysninger om formodede bivirkninger, som de har fået kendskab til, til EudraVigilance-databasen.

Lægemiddelstyrelsen har ved besvarelsen lagt til grund, at der spørges til en stigning i antallet af registrerede indberetninger om formodede bivirkninger ved HPV-vaccine.

Nedenfor er antallet af modtaget indberetninger fra piger/kvinder, hvor hvert symptom[5] indgår, opgjort pr. kalenderår i perioden 1. januar 2009 – 30. september 2015[6]. Endvidere er der indsat antallet af solgte vaccinedoser pr. år.

I tabellen er der medtaget tal for POTS, CRPS og Fibromyalgi.

Årstal	2009	2010	2011	2012	2013	2014	2015*	Total
Svimmelhed	16	3	7	18	158	69	286	557
Besvimelse	9	0	0	3	49	30	134	225
Ledsmerter	5	4	2	2	72	32	172	289
Træthed	14	3	5	4	126	64	356	572
Træthedssyndrom	0	0	0	0	4	2	2	8
POTS	1	0	0	0	21	18	28	68
CRPS	0	0	0	0	1	0	3	4
Fibromyalgi	0	0	0	0	1	4	9	14
Antal solgte doser	347.690	151.476	163.374	349.730	488.224	114.467	36.191	1.651.152

*1/1-30/9 2015, for solgte doser 1/1-30/6

Tallene i tabellen ovenfor er opgjort på baggrund af registreringstidspunktet, dvs. det tidspunkt hvor Lægemiddelstyrelsen har modtaget og registreret bivirkningsindberetningen. Tabellen viser, at antallet af indberetninger med de nævnte symptomer (svimmelhed, besvimelse, ledsmerter og træthed) er steget fra 2013 og fremefter. Der er modtaget flest indberetninger med de omhandlede symptomer i 2015.

I september 2015 offentliggjorde Sundhedsstyrelsen[7] (nu Lægemiddelstyrelsen) en tabel over de modtagne bivirkningsindberetninger i perioden 2009 til og med 30. juni 2015, opgjort på baggrund af tidspunktet for bivirkningsstart. Denne opgørelse viser, at der er modtaget flest indberetninger med bivirkningsstart i 2013, dernæst i 2012 og 2009. Det er de år, hvor der er solgt flest doser.

Én bivirkningsindberetning kan indeholde flere formodede bivirkninger, f.eks. kan en pige/kvinde med svimmelhed også have indberettet ledsmerter og/eller POTS.

Har man i de respektive lande set en øgning af ME-træthedssyndrom, POTS, eller andre tilsvarende sygdomme?

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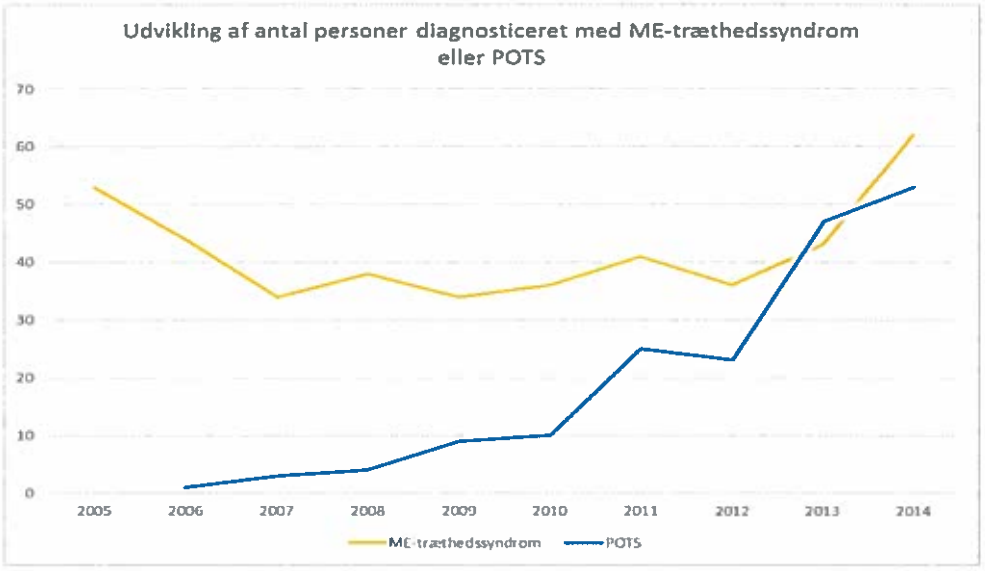
[5] Symptomerne i tabellen samt de tilsvarende MedDRA koder, der er fremsøgt i databasen angivet i parentes: Svimmelhed ("dizziness", "dizziness exertional", "dizziness postural", "vertigo" og "vertigo positional"), besvimelse ("syncope"), ledsmerter ("arthralgia"), træthedssyndrom ("chronic fatigue syndrome" (CFS) og "post viral fatigue syndrome" (ME)), træthed, herunder kronisk træthed ("fatigue"), POTS ("Postural Orthostatic Tachycardia Syndrome"). Det fremgår af tabellen, at der i alt er 68 tilfælde af POTS i den danske bivirkningsdatabase. Heraf er diagnosen stillet i 57 antal af indberetningerne, mens pigerne fortsat er i udredning eller medicinsk bekræftelse er endnu ikke hentet i 11 af indberetningerne. CRPS ("Complex Regional Pain Syndrome"), fibromyalgi ("fibromyalgia").

6 HPV-vaccinen Gardasil er siden 2009 indgået i det danske børnevaccinationsprogram.

[7] I Nyt om Bivirkninger, Lægemiddelstyrelsens elektroniske nyhedsblad, som kan ses via www.sst.dk. - https://sundhedsstyrelsen.dk/da/nyheder/2015/~/media/31C8B1F3E6734E54A95922C2385EA5B1.ashx

Sundhedsstyrelsen har som led i bidrag til besvarelse indhentet data fra Sundhedsdatastyrelsen. Data præsenteret i figuren er fremkommet ved udtræk af diagnoser fra Landspatientregistret (LPR).

Figur 1 herunder viser antal personer registret i LPR med henholdsvis POTS eller ME-træthedssyndrom diagnosen i perioden 2005 til 2014.



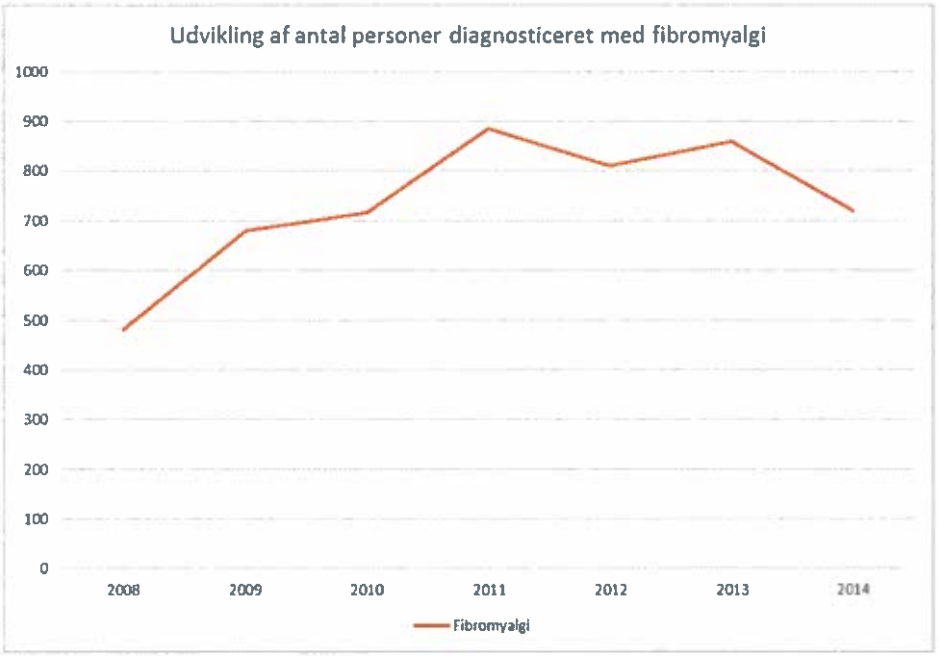
Figur 1: Antal personer diagnosticeret med ME-træthedssyndrom eller POTS i Danmark

Figuren viser, at der for begge grupper er tale om sjældne diagnoser. Der ses over hele perioden stigning i antal personer, der registreres i LPR med POTS diagnosen. Stigningen er mest markant for årene 2012 til 2014.

For ME-træthedssyndrom registreres det højeste antal personer med diagnosen hhv. i begyndelsen og slutningen af perioden.

Da der for begge diagnosers tilfælde er tale om sjældne diagnoser, kan ændring i registreringspraksis blandt sundhedspersonale forårsage store udslag i antal årligt registrerede tilfælde.

Figur 2 viser antallet af fibromyalgi diagnoser fra LPR for årene 2008 til 2014. Diagnosen blev oprettet i LPR i 2008.



Figur 2 Antal personer diagnosticeret med fibromyalgi i Danmark

Fibromyalgi diagnosen registeres i LPR med langt større hyppighed end ME-træthedssyndrom og POTS.

Antallet af fibromyalgi diagnoser var stigende indtil 2011, hvor det højest antal blev diagnosticeret, herefter har antallet været faldende.

3.11.2015

Dnr
005100/00.04.05/2015

The Danish Medicines Agency

Question E 9/2015 from the Nordic Council regarding adverse reactions to HPV-vaccine

Contribution from Finland to the question from the Nordic Council

Adverse reactions observed in Finland are entered into the Adverse Drug Reaction Register of Fimea, where both healthcare professionals and consumers can report any suspected or observed adverse reactions related to drugs or vaccines. In addition, under section 12 b of the Communicable Diseases Act (583/1986), the health care professionals should report all diagnosed or suspected adverse reactions related to a vaccine that come to their attention to the National Institute for Health and Welfare (THL), which is responsible for the procurement of vaccines, advising on their use and measurement of the impact (i.e. effectiveness and safety of the national immunisation programme in Finland).

The Adverse Drug Reaction Register of Fimea contains all adverse reactions related to HPV-vaccines reported to either directly to Fimea or to the THL and contains adverse reactions reported by both the health care professionals and by the consumers. The primary purpose of the reporting system is to serve as a signal detection tool, i.e. to detect previously unknown rare adverse reactions. Therefore, health care professionals are advised to report especially serious adverse reactions, unexpected reactions and reactions to newly marketed medicinal products. It is well known that reporting frequency may vary e.g. according to the extent of the use of a product, its novelty and any media attention around the disease the drug/vaccine is intended to alleviate or prevent, or the product itself.

HPV-vaccination (Cervarix) was introduced into the national immunisation programme in Finland in November 2013 with a 3-dose schedule. The target group is girls from 11-12 years of age with a catch-up in girls 13-15 years of age during the first 2 years of the programme. Before this large scale use, HPV-vaccines were available since 2006 in the Finnish market for immunisation on patients' own initiative at own cost, except on the island of Åland, where this autonomous district had chosen to vaccinate girls with Gardasil prior to the rest of Finland. According to estimations, a total approximate of 30 000 doses were given prior to November 2013. Also, both Gardasil and Cervarix had been used in approximately 40 000 subjects as part of a series of clinical trials carried out by University of Tampere with Professor Matti Lehtinen as PI in 2007-2009.

As of 12 September 2015, a total 279 648 doses of HPV vaccines has been delivered with a mean 60 % coverage for the first dose in the Finnish

national immunisation programme. The regional differences in vaccine coverage are quite wide.

By 26th of Oct 2015, a total of 205 cases were reported to the Adverse Drug Reaction register of Fimea related to adverse effects of HPV-vaccines. Of these, 191 cases were related to Cervarix and 14 cases to Gardasil. Before the launch of the vaccination programme there were 15 adverse effects reported related to HPV vaccines, after the launch, in 2013 Nov-Dec 24 reports, in 2014 124 reports and in 2015 Jan-Oct 42 reports. There is thus no evident trend observed in the increase in amount of adverse effects reported in Finland.

Of the reports, 164/205 were assessed as non-serious and 41/205 as serious. Most of the reports described vaccination site reactions and symptoms of the vaccinated limb, syncope and dizziness as a response to the needle injection, fever, headache and allergic reactions, all previously recognised adverse effects of vaccination. A total of 6 cases reported to Adverse Drug Reaction Register of Fimea described chronic fatigue syndrome, POTS, or diverse neurological and fatigue symptoms, all reports received after Feb 2015.

THL is responsible for the Hospital Discharge Register (HILMO), which includes all the diagnoses made in hospital wards and hospital outpatient clinics. THL reviewed the PANS (Pediatric acute-onset neuropsychiatric syndrome) and POTS (Postural orthostatic tachycardia syndrome) related ICD10 diagnostic codes (G93.8, F42.8, I49.8) among those below 18 years of age during years 2010-2013 reported to HILMO. Incident cases with codes G93.8 and F42.8 varied annually between 20 to 41 and between 41 to 79 with code I49.8. When reviewing the incident cases from 2000 to 2009, there was no indication of increasing trend. In similar analyses of CFS (Chronic fatigue syndrome) /ME (Myalgic encephalomyelitis) /SEID (Systemic exertion intolerance disease) related ICD10 diagnosis G93.3, the observed reported numbers have remained similarly in the expected range.

For more information please contact Ms Liisa Näveri, tel. +358 29 522 3340, email: liisa.naveri@fimea.fi.

Director General — Sinikka Rajaniemi

Head of Division, Pharmacovigilance — Liisa Näveri

Camilla Riesbeck - 9744

Fra:	Guðrún Kristín Steingrímsdóttir <gudrun.kristin.steingrimsdottir@lyfjastofnun.is>
Sendt:	3. november 2015 13:03
Til:	Camilla Riesbeck - 9744; HENRIK G. JENSEN
Cc:	Sigríður Ólafsdóttir; Kolbeinn Guðmundsson; Rúna Hauksdóttir Hvannberg; Hrefna Guðmundsdóttir
Emne:	RE: Lægemiddelstyrelsen (DK) anmoder om bidrag til besvarelse af spørgsmål E 9/2015 fra Nordisk Råd om bivirkninger ved HPV-vaccine
Vedhæftede filer:	IMA Cervarix reported ADRs in Iceland.docx
Kategorier:	GoPro Portal: Gemt under sagstype: 2015103451 - SUM anmoder LMS om at koordinere svar på spørgsmål fra Nordisk Råd vedr. HPV-v...
Sent to GoPro Portal:	-1

Good morning

It is in the hands of The Directorate of Health to oversee vaccinations in Iceland (http://www.landlaeknir.is/english/). According to information received from the Chief Epidemiologist for Iceland, for the HPV vaccines the agency has recommended ADRs to be reported directly to the Icelandic Medicines Agency. All reported ADRs should therefore have been received by the IMA. Reports of suspected ADRs of vaccines are handled the same way as other ADR reports at the IMA.

A summary document of the relevant ADRs received by the IMA has been attached to this e-mail. A total of 10 reports have been received from 2011 until present, including one classified as serious (No. 10 on the attached list). Cervarix and Gardasil are marketed in Iceland but all the reported events regard Cervarix.

Unfortunately it is not possible for the IMA to access information regarding whether there is an increased frequency of cases of girls/women "med svimmelhed, besvimelse eller ledsmerter samnt træthedssyndrom", in Iceland. Furthermore at this point in time we do not have any data available to conclude whether there has bee "øgning af ME-træthedssyndrom, POTS, eller andre tilsvarende sygdomme". For this information it might be helpful to contact The Directorate of Health.

With best regards;
Guðrún

Guðrún Kristín Steingrímsdóttir, Cand. odont.
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www.lyfjastofnun.is

1. Reported by a physician. **(2011)**
   Cervarix injection. A few minutes later the girl turned pale and felt dizzy. She felt a knot in her throat, possibly mild difficulties breathing. Her extremities went cold, heart rate increased (approximately 100), blood pressure normal. Received adrenalin i.m. and steroids i.v. approx. 15 minutes later, despite her blood pressure being normal. She was transferred to the Department of Pediatrics, National University Hospital of Iceland (Barnaspítali Hringsins) but had recovered by the time she arrived. Physicians at Barnaspítali Hringsins interpreted this to be a vasovagal reaction or a mild allergic reaction. The patient had received the first Cervarix injection one month previously with no problems.
   - Vertigo (dizziness)
   - Dysphoria (general discomfort)
   - Lump in throat
   - Mild difficulties breathing
   - Cold extremities
   - Increased heart rate

2. Reported by a healthcare professional. **(2011)**
   The patient´s mother reported that the patient had experienced abdominal pain, pain in the navel area, and nausea following her 2nd injection with Cervarix. She had also experienced the same symptoms following the first injection.
   - Abdominal pain
   - Nausea

3. Reported by a healthcare professional. **(2011)**
   The reporter gave the patient her 2nd Cervarix injection. Moments later she went pale and felt dizzy, had to lie down. She proceded to experience abdominal pain and gagged several times. Next a headache and an allergic reaction in her throat. It took her two hours to recover. Had no problems after the 1st injection.
   - Vertigo (dizziness)
   - Abdominal pain
   - Nausea
   - Headache
   - Allergic reaction in throat

4. Reported by a school nurse. **(2012)**
   Symptoms were still present and strong 24 hours after the vaccination. IMA requested further information but did not receive an answer.
   - Severe vertigo
   - Headache
   - Nausea

5. Reported by a physician at pediatric emergency department at the National University Hospital of Iceland. **(2012)**

Patient got urticaria rash and inflamed joints in mcp joints 2-3 bilat and joint pain in mtp joints bilat. This was 3 days after the vaccination.

- Urticaria rash
- Inflamed joints
- Joint pain

6. Reported by general public. **(2013)**
   Report from mother of patient. Patient received 3rd vaccination with Cervarix in the morning at school, left school around noon with fever and severe headache. Has a fever and severe headache for the rest of the day and vomits around six pm and again right before midnight. Feels much better the next day but stays home.
   - Severe headache
   - Fever
   - Vomiting

7. Reported by a school nurse. **(2013)**

This was her 3rd vaccination. Did not experience any real symptoms after the first two vaccinations.

- High fever
- Vertigo
- Tremor
- Weakness
- Headache
- Nause
- Sweating
- Reduced appetite

8. Reported by a school nurse. **(2013)**

Her hand felt bad after Cervarix injection and discomfort in entire body for the rest of the day and for part of the next day. Felt dizzy and strange.

- Felt sluggish
- Weakness
- General discomfort
- Vertigo

9. Reported by a school nurse. **(2014)**

Has received 3 Cervarix vaccinations and after each she has felt weak, got a fever, headache and abdominal pain. It has taken over 24 hours to recover each time.

- Weakness
- Fever
- Headache
- Abdominal pain

10. Reported by a physician at the Department of Pediatrics, National University Hospital of Iceland (Barnaspítali Hringsins) . **(2015)**

Had a „fit" where she lost all strength in her extremities. This happened over 30 minutes in the evening, she couldn´t move. She could move her head and her breathing was normal. Went to the hospital, still in this state. Was admitted for observation. Recovered after appr. 4 hours and was discharged the following morning. She had received her 3rd vaccination with Cervarix two weeks earlier. This was registered as a serious ICSR.

- Muscle Weakness – with episode of loss of strength in all the extremities.

Spørsmål:

De nordiske ministre bedes redegøre for, hvordan man i deres respektive lande registrerer bivirkninger til HPV vaccinen, samt hvor mange bivirkninger der er registreret

Svar:

I Norge ble vaksinering mot HPV-viruset innført i 2009. Det er vaksinen Gardasil som benyttes.

Bivirkningsmeldesystemet foregår ved at helsepersonell sender meldinger på papir til Folkehelseinstituttet (FHI). FHI gjør en vurdering av årsakssammenheng for hver enkelt melding og innhenter ytterligere informasjon fra melder når dette er nødvendig. Resultatet av vurderingen sendes tilbake til melderen. Bivirkningsmeldingen legges inn i den norske bivirkningsdatabasen, som kommuniserer med andre internasjonale databaser, som den europeiske bivirkningsdatabasen (EudraVigilance).

For meldinger knyttet til HPV-vaksinen gjøres det i tillegg ekstra oppfølging hos FHI dersom det meldes om langvarige bivirkninger (der utfall ikke er oppgitt eller symptomene er meldt som fortsatt pågående) . Et eget oppfølgingsskjema er utarbeidet og sendes den som har meldt, der det blant annet spørres om utfall, om symptomer før vaksinering, hvordan daglig aktivitet påvirkes, annen medisinbruk etc.

Meldeordningen for *pasienter* er nettbasert og meldingene sendes elektronisk direkte til Legemiddelverket. Pasientmeldingene er anonyme. Det vil derfor ikke være mulig for Legemiddelverket å kontakte pasienten i ettertid for å innhente mer informasjon, eller gi individuell tilbakemelding.

Alvorlige bivirkningsmeldinger som kommer inn i den norske bivirkningsdatabasen sendes videre til EudraVigilance og aktuell MT-innehaver. Denne oversendelsen gjøres alle virkedager. For å bli definert som en alvorlig bivirkning må meldingen oppfylle ett eller flere av følgende kriterier: medført sykehusinnleggelse eller forlenget sykehusopphold, regnes som en medisinsk viktig hendelse, gitt vedvarende betydelig nedsatt funksjonsevne eller funksjonskapasitet, livstruende sykdom eller død.

Hos Legemiddelverket har vi særskilt overvåking av mistenkte bivirkninger etter vaksinering mot HPV som kan skyldes autonom dysfunksjon, slik som POTS o.l. Hver måned gjennomgås de sist innkomne bivirkningsmeldingene samt hvilke symptomer som er meldt for å kunne fange opp denne typen mistenkte bivirkninger.

I den norske bivirkningsdatabasen er det per 28.10.15 totalt registrert 2360 mistenkte bivirkninger/symptomer etter vaksinering med Gardasil. Disse er fordelt på totalt 620 bivirkningsmeldinger, ettersom hver melding kan inneholde flere bivirkninger/symptomer. Av disse er 44 (7 %) klassifisert som alvorlige. Det er ingen meldte bivirkninger etter vaksinering med Cervarix.

Legemiddelverket gir ut oversikter over antall meldte bivirkninger etter vaksinering mot HPV to ganger per år i samarbeid med Folkehelseinstituttet. Her gis det en oversikt over vaksinasjonsdekningen, hva om er meldt av bivirkninger innenfor hver system-organklasse

samt en egen gjennomgang av de alvorlige meldingene. Den siste halvårlige rapporten er fra juni 2015 (ligger vedlagt, samt kan finnes via lenke nederst på følgende nettside).

http://www.legemiddelverket.no/Nyheter/Bivirkninger/Sider/Bivirkningsmeldinger-for-HPV-vaksinen-Gardasil---oppdaterte-tall-per-23.-juni-2015.aspx

Spørsmål:

Har man i de respektive lande set en stigning i antallet af tilfælde, hvor man har registreret piger/kvinder med svimmelhed, besvimelse eller ledsmerter samt træthedssyndrom?

Har man i de respektive lande set en øgning af ME-træthedssyndrom, POTS, eller andre tilsvarende sygdomme?

Svar:

Det kommer ikke tydelig frem om det spørres etter økning blant landets innbyggere generelt sett, eller om det spørres etter en økning i bivirkningsmeldinger etter vaksinering.

Populasjonsnivå:

I Norge ble det gjennomført økt overvåking fram til 1. september 2010, slik det rutinemessig gjøres når nye vaksineprogrammer starter. Det er derfor et økt antall bivirkningsmeldinger i årene 2009 og 2010.

Det er ikke gjort populasjonsstudier der man sammenligner forekomst av ovennevnte symptomer (svimmelhet, besvimelser, leddsmerter eller tretthetssyndrom) blant HPV-vaksinerte mot uvaksinerte, og man kan derfor ikke si noe om det er endring i forekomst mellom disse to gruppene. Derimot er det foretatt en registerstudie for å kartlegge forekomst (insidens) av ME/CFS etter alder og kjønn i Norge 2008-2012, (Bakken et. al,). Der fant man at kvinner har høyere risiko for å rammes av ME/CFS enn menn, og at symptomdebut sees hyppigere i enkelte aldersgrupper.

Det finnes også en studie som så på risiko for ME/CFS etter influensainfeksjon eller vaksinasjon med Pandemrix® under pandemien (Influensa A H1N1pdm09) (se Magnus et. al.). Her fant man at det ikke var økt risiko for ME/CFS blant vaksinerte, men økt risiko for ME/CFS etter influensainfeksjon.

Meldte hendelser etter vaksinering med Gardasil:

Det gjøres oppmerksom på at meldinger av bivirkninger i meldesystem slik som dette ikke kan bruke som grunnlag for å se på endringer i frekvens, slik man kan i kliniske studier. Det er mange faktorer og tilfeldigheter som påvirker hvorvidt en bivirkningsmelding blir sendt inn eller ikke. Bivirkningsmeldinger/spontanrapporter gir imidlertid verdifull informasjon om eventuelle nye bivirkninger som oppstår. Det er også viktig å være klar over at en årsakssammenheng ikke er etablert på meldetidspunktet, ettersom en bivirkningsmelding sendes inn på *mistanke* om en sammenheng mellom legemidlet og det oppståtte symptomet/sykdommen.

Symptomene listet overfor (svimmelhet, besvimelser) blir rapportert for flere typer vaksiner, og skyldes som oftest en vasovagal reaksjon, som blant annet utløses ved skremmende eller ubehagelige sanseinntrykk (for eksempel injeksjonsprosedyren). Typiske vasovagale symptomer er svimmelhet, blekhet, kvalme, lav puls, kortvarig blodtrykksfall og i noen tilfeller besvimelse. Det er viktig ved tolkning av data i meldingene at man også ser på varighet av symptomene.

Vedlegg:
1: Bivirkninger av HPV-vaksine (Gardasil) – oppdaterte bivirkningstall per 23. juni 2015
2: Bakken et. al, 2014
3: Magnus et. al, 2015

Bivirkninger av HPV-vaksine (Gardasil) – oppdaterte bivirkningstall per 23. juni 2015

Vaksinen mot humant papillomavirus (HPV) beskytter mot de typene av HPV som er årsaken til utvikling av ca 70 % av livmorhalskrefttilfellene. Vaksinen ble i løpet av skoleåret 2009/2010 innført som en del av barnevaksinasjonsprogrammet for jenter på 7. klassetrinn. Vaksinen gis i tre doser i løpet av 6-12 måneder (1). I Norge benyttes HPV-vaksinen Gardasil.

Oversikt over antall vaksinerte jenter per 23. juni 2015* (1):

Jenter født i 1999	1. dose	2. dose	3. dose
Antall doser satt	25550	25212	24420
Prosentandel vaksinerte	82 %	81 %	78 %

Jenter født i 2000	1. dose	2. dose	3. dose
Antall doser satt	25960	25451	23721
Prosentandel vaksinerte	83 %	82 %	76 %

Jenter født i 2001	1. dose	2. dose	3. dose
Antall doser satt	25780	25420	24224
Prosentandel vaksinerte	86 %	85 %	81 %

Jenter født i 2002	1. dose	2. dose	3. dose
Antall doser satt	25484	25009	22444
Prosentandel vaksinerte	86 %	85 %	76 %

*Vaksinasjonstall for jenter født i 1997 og 1998 publiseres av Folkehelseinstituttet sammen med ordinær dekningsstatistikk for alle vaksinene i barnevaksinasjonsprogrammet.

Totalt er det gitt 436 838 doser HPV-vaksine til jenter født fra og med 1997 til og med 2002 (1).

Det er så langt i vaksinasjonsprogrammet meldt inn 581 bivirkningsmeldinger etter at ca. 150 000 jenter er vaksinert. I all hovedsak (94 %) betegnes bivirkningene som lite alvorlige. Folkehelseinstituttet oppfordret det første året til at *alle* bivirkninger av HPV-vaksinen ble meldt, slik det er vanlig for nye vaksiner, og HPV-vaksinene Gardasil og Cervarix stod på Legemiddelverkets overvåkingsliste inntil høsten 2010.

Antall bivirkningsmeldinger fordelt på år

År	2009*	2010*	2011	2012	2013	2014
Totalt antall meldinger (antall alvorlige)	101 (2)	131 (9)	91 (9)	84 (6)	58 (1)	78 (3)

*) Utvidet overvåking september 2009 – september 2010

Totalt antall rapporter, inkludert alvorlige bivirkninger	**581**
Antall rapporter med mistenkte alvorlige** bivirkninger	**37**

**For å bli definert som en alvorlig bivirkning må meldingen oppfylle et eller flere av følgende kriterier: medført sykehusinnleggelse eller forlenget sykehusopphold, regnes som en medisinsk viktig hendelse, gitt vedvarende betydelig nedsatt funksjonsevne eller funksjonskapasitet, livstruende sykdom eller død (Legemiddelverket har ikke fått melding om dødsfall som kan knyttes til HPV-vaksinen).

De vanligste meldte bivirkningene av HPV-vaksinen er hevelse og ømhet i armen der vaksinen er satt, feber, hodepine, kvalme, oppkast, diaré og magesmerter (se tabellen under). Allergiske reaksjoner på vaksinen forekommer i sjeldne tilfeller. Besvimelser og nesten-besvimelser, med eller uten kramper og pustebesvær (hyperventilering), er ikke uvanlig ved vaksinering, og kan skyldes smerter eller ubehag ved vaksinering eller omstendighetene rundt.

De 37 alvorlige bivirkningene som er rapportert ved bruk av Gardasil, er hovedsakelig tilfeller der jentene ble lagt inn på sykehus på grunn av sine reaksjoner (besvimelse, kramper eller allergi). Utover dette er følgende alvorlige tilfeller rapportert inn:

- Et tilfelle av meningoencefalitt (betennelse i hjernen) med status epilepticus (gjentatte epileptiske anfall med lenger varighet). Jenta hadde fått Gardasil og en annen vaksine flere måneder før hendelsen, og det er vurdert som lite sannsynlig at det er sammenheng mellom vaksinen og hendelsen.
- Fire tilfeller med nevrologiske symptomer: Et tilfelle av forbigående tap av en del av synsfeltet på det ene øyet og ett tilfelle av redusert syn med ukjent forløp. Synspåvirkning er en sjelden hendelse hvor sammenheng med vaksinering ikke kan utelukkes, men en eventuell årsakssammenheng er meget usikker, et tilfelle av epileptisk anfall kort tid etter vaksinering. Det kan ikke utelukkes at vaksineringen kan ha vært medvirkende årsak til anfallet. To tilfeller av lammelser i ansiktet som har oppstått 2-3 uker etter vaksinering. I det ene tilfellet finnes det andre mulige årsaker til lammelsen, men det kan ikke utelukkes at vaksinering kan ha medvirket til lammelser hos disse jentene.
- Et tilfelle av cyste på en eggstokk, fem uker etter vaksinasjon. Dette er en sjelden hendelse hvor sammenheng med vaksinering ikke kan utelukkes, men en eventuell årsakssammenheng er meget usikker.
- Fem tilfeller av postviralt tretthetssyndrom/kronisk utmattelsessyndrom /myalgisk encefalomyelitt (ME). Det ene tilfellet er ikke meldt av helsepersonell, og en eventuell årsakssammenheng med vaksinen er derfor ikke vurdert. I et annet tilfelle er årsakssammenheng vurdert som mulig, men det nevnes i vurderingen at det generelt sett ikke er påvist noen årsakssammenheng mellom symptomer på utmattelse og HPV-vaksinen. I de siste tre tilfellene er andre årsaker vurdert som mer sannsynlige.
- Ett tilfelle der ei jente opplevde en rekke reaksjoner som påvirket generell livskvalitet og som påvirket prestasjoner på skolen og i andre aktiviteter. Hendelsen er ikke vurdert av helsepersonell og det avventes mer informasjon for å vurdere en eventuell årsakssammenheng.

- Et tilfelle hvor en jente hovnet opp i ansiktet og fikk pustebesvær om kvelden etter at hun fikk vaksinen. Jenta er allergiker. Det er vanskelig å si med sikkerhet om vaksinen har vært årsaken til symptomene.
- Det er fire tilfeller der jentene er under utredning eller man venter på mere informasjon: To tilfeller med bl.a. besvimelser, et tilfelle med mistenkt kronisk utmattelsessyndrom under utredning og et tilfelle hvor en pike opplevde vekselvis rask puls og generelt ubehag, nå i bedring.

I all hovedsak er pasientene i bedring eller er helt friske igjen ved rapporteringstidspunktet Innrapportere bivirkninger så langt er som forventet, og gir ingen grunn til å endre på gjeldende anbefalinger om bruk av vaksinen. I all hovedsak meldes det om kortvarig ubehag i forbindelse med vaksineringen. Legemiddelverket fortsetter å følge nøye med på bivirkningsrapporteringen for Gardasil.

Symptomer rapportert etter vaksinasjon, per 23. juni 2015

Hovedgrupper	Antall reaksjoner
Generelle symptomer og reaksjoner på administrasjonsstedet Eks: Smerter på injeksjonsstedet, ubehag, feber	565
Nevrologiske symptomer Eks: Hodepine, svimmelhet, bevissthetstap, nummenhet, kramper	479
Mage-tarmsymptomer Eks: Magesmerter, kvalme, brekninger, diaré	364
Hudsymptomer Eks: Utslett, kløe, rødhet	250
Muskelskjelettsymptomer Eks: Muskelsmerter, leddsmerter, muskelstivhet	137
Psykiatriske symptomer Eks: Søvnforstyrrelser, rastløshet, tiltaksløshet, engstelse	112
Karsymptomer Eks: Rødming, blekhet	86
Luftveissymptomer Eks: Pustevansker, tungpustet, hyperventilering, hoste, irritasjon i luftveiene	66
Øyesymptomer Eks: Synsforstyrrelser, midlertidig, delvis synstap, hevelse, rødhet, irritasjon i øyet	35
Infeksjoner Eks: Lungebetennelse, herpesvirusinfeksjon	17
Stoffskifte- og ernæringsbetingede symptomer Eks: Redusert appetitt	18
Endringer i laboratoriesvar Eks: Unormal puls eller pusterytme	15
Symptomer fra blod- og lymfesystemet Eks: Hevelse i lymfekjertler	10
Hjertesymptomer Eks: Cyanose (blå i huden), langsom hjerterytme	9
Symptomer relatert til kjønnsorganene Eks: Genital blødning, uregelmessig menstruasjon	9
Øresymptomer Eks: Ubehag i øret	7

Sosiale forhold Eks: Synsvansker	4
Prosedyremessig komplikasjon Eks: Smerte ved injeksjonssted	3
Svulster, godartede og ondartede Eks: Vorter	1
Symptomer fra immunsystemet Eks: Allergisk reaksjon	1
Totalt	**2188*** **

*** Antallet reaksjoner er høyere enn antall meldinger, fordi hver melding kan omtale flere bivirkningssymptomer/-reaksjoner.

Referanser:

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BMC Medicine

RESEARCH ARTICLE Open Access

Two age peaks in the incidence of chronic fatigue syndrome/myalgic encephalomyelitis: a population-based registry study from Norway 2008–2012

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Abstract

Background: The aim of the current study was to estimate sex- and age-specific incidence rates of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) using population-based registry data. CFS/ME is a debilitating condition with large impact on patients and their families. The etiology is unknown, and the distribution of the disease in the general population has not been well described.

Methods: Cases of CFS/ME were identified in the Norwegian Patient Register (NPR) for the years 2008 to 2012. The NPR is nationwide and contains diagnoses assigned by specialist health care services (hospitals and outpatient clinics). We estimated sex- and age-specific incidence rates by dividing the number of new cases of CFS/ME in each category by the number of person years at risk. Incidence rate ratios were estimated by Poisson regression with sex, age categories, and year of diagnosis as covariates.

Results: A total of 5,809 patients were registered with CFS/ME during 2008 to 2012. The overall incidence rate was 25.8 per 100,000 person years (95% confidence interval (CI): 25.2 to 26.5). The female to male incidence rate ratio of CFS/ME was 3.2 (95% CI: 3.0 to 3.4). The incidence rate varied strongly with age for both sexes, with a first peak in the age group 10 to 19 years and a second peak in the age group 30 to 39 years.

Conclusions: Early etiological clues can sometimes be gained from examination of disease patterns. The strong female preponderance and the two age peaks suggest that sex- and age-specific factors may modulate the risk of CFS/ME.

Keywords: Chronic fatigue syndrome, Myalgic encephalomyelitis, Incidence rate, Sex, Age

Background

Chronic fatigue syndrome (CFS), or myalgic encephalomyelitis (ME), is a debilitating, medically unexplained condition [1]. The terms CFS and ME are often used interchangeably, and Norwegian health authorities recommend using the combined term CFS/ME [2].

CFS/ME is an unspecific condition for which it has been difficult to establish objective medical criteria, and the CFS/ME diagnosis has been debated in the medical community for many years [3]. Symptoms may fluctuate and vary in intensity within and among patients, but persistent or relapsing fatigue is always present [4]. Functional status and wellbeing are often strongly affected [5].

While the etiology of CFS/ME remains largely unknown, several trigger mechanisms have been proposed, including infections, stress and trauma [1]. A sudden increase in CFS/ME was reported following a large waterborne outbreak of giardiasis in Bergen, Norway, in 2004 [6]. Autoimmune etiology has also been suggested, based on the observation that B-lymphocyte depletion with the monoclonal anti-CD20 antibody rituximab was associated

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with transient symptom improvement in some patients with CFS/ME [7].

Due to terminological variations and diagnostic inconsistencies, it is difficult to assess the prevalence and incidence rate of CFS/ME in a population. Overall prevalence estimates vary from 0.1% to 2.5%, depending on the criteria applied [1,8].

The aim of the current study was to estimate sex- and age-specific incidence rates of CFS/ME in Norway during a five-year period, using data from a nationwide registry containing diagnoses assigned by Norwegian specialist health care services (hospitals and outpatient clinics).

Methods

The use of national data and data linkage procedures were approved by the Regional Committee for Medical and Health Research Ethics, South-East Norway. The ethical approval permitted the use of national level data. The research group did not at any time point have access to names or personal identification numbers, and all data storage and handling have been carried out within strict standards to ensure data privacy and protection.

The study population was the complete Norwegian population five years old and older as of 1 January 2008, registered in the Central Population Registry. For each individual we had access to information on vital status (dates for emigration or death) for the entire study period, 2008 to 2012. All individuals were assigned a study allocation number based on the 11-digit personal identification number unique to all Norwegian citizens and migrants with legal residence in Norway.

Information on CFS/ME was obtained from the Norwegian Patient Register (NPR), which is a database containing data from all Norwegian hospitals and outpatient clinics. For each hospitalization or outpatient visit, reporting of data to the NPR is mandatory and is linked to the reimbursement system. Discharge diagnoses are reported as International Classification of Disease, version 10 (ICD-10) codes. Personal identification numbers have been reported to the NPR from 2008 onwards, making tracking of subjects possible for research purposes. Reporting of the personal identification number has been nearly complete from the start [9]. The personal identification number is stored in encrypted form in the NPR.

Cases of CFS/ME were all in- and outpatients in Norwegian hospitals who were registered with the ICD-10 code G93.3 ('postviral fatigue syndrome/benign myalgic encephalomyelitis'). Data from mental health care facilities were not included. In addition to the ICD-code, the NPR provided information about sex, year of birth, dates for hospitalizations and outpatient visits, and a study allocation number for data linkage. The first registered G93.3 episode for each patient was used in the analyses.

Age was calculated as the age in 2008 by subtracting year of birth from calendar year. We estimated sex- and age-specific incidence rates by dividing the number of new cases of CFS/ME in each sex/age category by the total number of person years at risk in the same category. Time at risk for each individual was calculated by using the information on vital status. Age was categorized in five-year intervals (5 to 9, 10 to 14, ..., 55+). We estimated the incidence rate ratio of CFS/ME by applying Poisson regression with sex, age categories, and year of diagnosis as covariates and compared estimated incidence rates in sex and age categories.

The Stata software package, Version 11.2 (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX, USA: StataCorp LP) was used for data analysis.

Results

During the years 2008 to 2012, 5,809 patients (75.4% women) five years old or older in 2008 were registered with CFS/ME. Figure 1 shows the number of cases in one-year age intervals for women and men separately. For both sexes, two distinct peaks in the number of cases were observed, the first in the age group 10 to 19 years and the second in the age group 30 to 39 years.

Table 1 shows the incidence rate of CFS/ME by year, sex and age category. The incidence rate was fairly stable over the years of follow-up. The overall incidence rate per 100,000 person years was 39.4 (95% confidence interval (CI): 38.2 to 40.6) for women, while the corresponding figure was 12.9 (95% CI: 12.3 to 13.6) for men. This gives an incidence rate ratio of 3.2 (95% CI: 3.0 to 3.4) for women compared to men. The incidence rate was highest in the age groups 10 to 14, 15 to 19, 30 to 34 and 35 to 39 years.

Figure 2 shows the number of cases per year by age category for men and women separately, estimated from the Poisson regression model. The non-overlapping CIs support the existence of two age peaks in the distribution indicated by the raw data (Figure 1).

Figure 3 shows the estimated incidence rate per 100,000 person years for men and women separately. After adjustment for population figures, the pattern with two age peaks is clear for women, whereas a second peak is not evident for men.

Repeating the analyses including a 'wash-out' period of two years (that is, excluding data for all patients first registered in 2008 and 2009) gave similar sex and age patterns as those described here (results not shown). Norway is divided into four health regions, with most people living in the South-East region. Although some variations were observed, the pattern with a strong preponderance of women and higher risk of CFS/ME in the

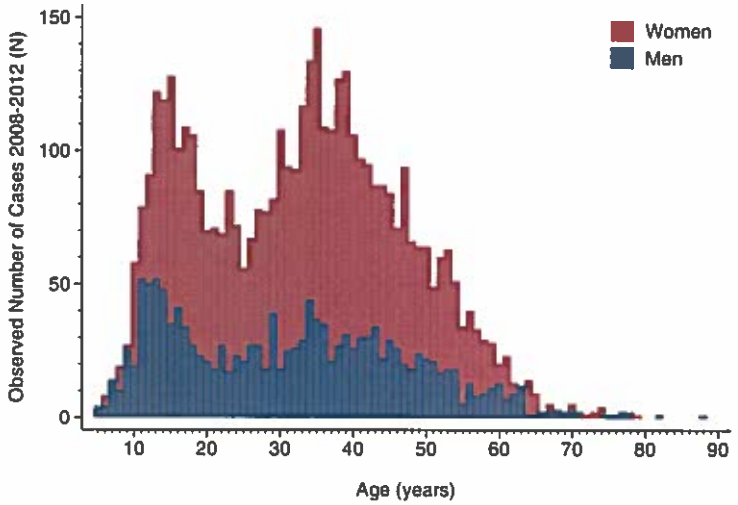

Figure 1 Observed number of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) cases by sex and one-year age groups (age in 2008). Data from the Norwegian Patient Register 2008 to 2012.

Table 1 Incidence rates and incidence rate ratios of CFS/ME in the Norwegian population according to year, sex and age in 2008 (categorized), 2008 to 2012

Variable	Number of cases	Number of person years	Incidence rate per 100,000 person years (95% CI)	Incidence rate ratio (95% CI)
Year				
2008	1,172	4,494,062	26.1 (24.6 to 27.6)	1.0 (ref.)
2009	1,113	4,491,822	24.8 (23.3 to 26.3)	0.9 (0.9 to 1.0)
2010	1,104	4,449,683	24.8 (23.4 to 26.3)	0.9 (0.9 to 1.0)
2011	1,222	4,395,325	27.8 (26.3 to 29.4)	1.0 (1.0 to 1.1)
2012	1,198	4,342,818	27.6 (26.1 to 29.2)	0.9 (0.9 to 1.1)
Sex				
Male	1,430	11,050,966	12.9 (12.3 to 13.6)	1.0 (ref.)
Female	4,379	11,122,744	39.4 (38.2 to 40.6)	3.2 (3.0 to 3.4)
Age category (years)				
5 to 9	121	1,497,289	8.1 (6.7 to 9.7)	1.3 (1.1 to 1.6)
10 to 14	690	1,578,106	43.7 (40.5 to 47.1)	7.1 (6.3 to 8.1)
15 to 19	689	1,598,802	43.1 (39.9 to 46.4)	7.0 (6.2 to 8.0)
20 to 24	473	1,481,322	31.9 (29.1 to 34.9)	5.2 (4.5 to 5.9)
25 to 29	492	1,523,923	32.3 (29.5 to 35.3)	5.2 (4.6 to 6.0)
30 to 34	688	1,603,520	42.9 (39.6 to 46.2)	7.0 (6.1 to 7.9)
35 to 39	771	1,809,970	42.6 (39.6 to 45.7)	6.9 (6.1 to 7.8)
40 to 44	614	1,797,270	34.2 (31.5 to 37.0)	5.6 (4.9 to 6.3)
45 to 49	496	1,636,483	30.3 (27.7 to 33.1)	4.9 (4.3 to 5.6)
50 to 54	383	1,564,478	24.5 (22.1 to 27.1)	4.0 (3.4 to 4.6)
55+	392	6,082,547	6.2 (5.6 to 6.9)	1.0 (ref.)

CFS/ME, chronic fatigue syndrome/myalgic encephalomyelitis; CI, confidence interval.

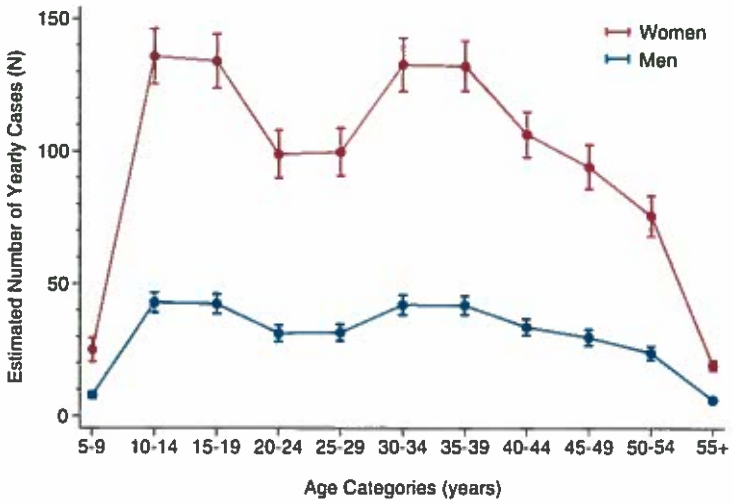

Figure 2 Number of yearly cases of CFS/ME by sex and five-year age groups estimated by Poisson regression analyses. CFS/ME, chronic fatigue syndrome/myalgic encephalomyelitis.

age groups 10 to 19 years and 30 to 39 years also persisted when performing the analyses for each health region separately (results not shown).

Discussion

This is the largest study to date of CFS/ME, including 5,809 patients and using national population-based registry data. To our knowledge, this is also the first study to investigate the distribution of CFS/ME by sex *and* age in a population. The main new finding is the distinct age peaks in the incidence of CFS/ME, with a first peak in the number of cases in the age group 10 to 19 years and a second peak in the age group 30 to 39 years. Although a higher prevalence in women than in men has been a consistent finding in previous studies [1], most epidemiological studies so far have been too small to report age distributions [10-15] or have only reported the age distribution for women and men combined [16,17].

The strength of the current study is the access to individual-level hospital data from an entire country, which could be linked to high-quality population data by means of personal identification numbers. In Norway, access to specialist health care services requires referral from a general practitioner, and the cases included in the NPR probably represent the more severe and established cases of CFS/ME. The Norwegian health care system is financed through governmental funding. All hospitalizations are free of charge, while outpatients 16 years old or older are

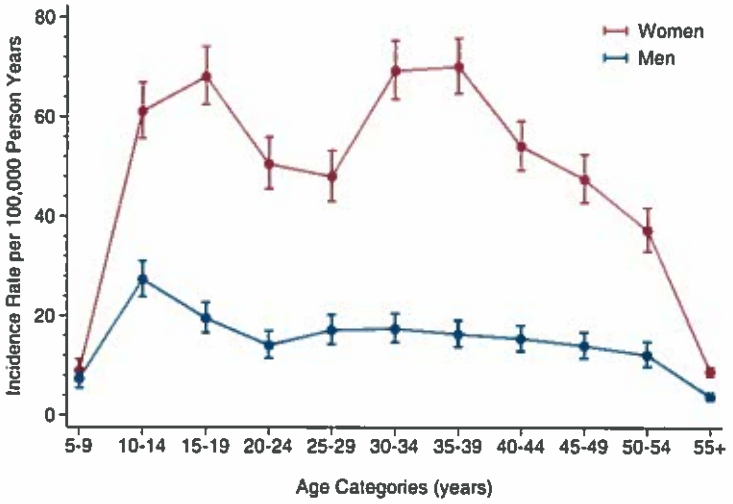

Figure 3 Estimated incidence rates of CFS/ME per 100,000 person years by sex and five-year age groups. CFS/ME, chronic fatigue syndrome/myalgic encephalomyelitis.

charged a minor fee. Thus, economic status should have little influence on patterns of seeking health care.

It is reasonable to assume that the more severe cases of CFS/ME are referred to specialist health care services, and that this is also the case for young patients and people with sudden onset of symptoms. Even so, the estimated incidence rates in the current study may differ from the true population incidence. Since our study is based on diagnoses reported from specialist health care services, we have calculated the incidence of being diagnosed with the condition and not the incidence of the condition as such. Also, some patients regarded as incident cases in the current study may have been diagnosed the first time before the start of follow-up. Such cases will contribute to an overestimation of the true incidence rate. On the other hand, patients with less severe CFS/ME are probably in many cases only diagnosed in the primary health care system, a mechanism that leads to underestimation of the incidence rate. However, it seems unlikely that such factors have severely biased the incidence rate ratio of women versus men or the incidence rate ratios of the different age categories seen in our study.

The main weakness of this study is the possible variation in the use of ICD-10 code G93.3 for CFS/ME due to the inherent heterogeneity of the disease. We did not have access to information from medical records and could not investigate the diagnostic criteria applied in individual patients. According to the recommendations from the Norwegian Directorate of Health, children with suspected CFS/ME should have the diagnosis confirmed by a pediatrician [2]. Thus, children receiving the diagnosis of CFS/ME are routinely referred to their local hospital for the diagnostic work-up. Complicated cases may be further referred to regional university hospitals. After the diagnosis of CFS/ME is made, patients are typically followed up in primary care. Adults may receive a diagnosis of CFS/ME after evaluation by a general practitioner. However, since the diagnosis requires that other possible diagnoses are ruled out, most patients have most likely also been seen by a specialist at a local hospital during the diagnostic work-up. Patients may also be referred to one of the four university hospitals which have specialized units for diagnosing CFS/ME or to the national CFS/ME-center at Oslo University Hospital. Follow-up after diagnosis is the responsibility of general practitioners.

The Norwegian Directorate of Health has stated that ICD-10 code G93.3 is to be used for this disorder [2]. However, cases in the present study come from a large number of different hospitals and the criteria used to diagnose CFS/ME might have varied. In a recent study, most Norwegian hospitals reported that they had used either the Canadian 2003 criteria [18] or the CDC 1994 criteria [4] when diagnosing CFS/ME in adults [19]. Pediatricians generally reported they follow the guidelines of the Norwegian Pediatric Association [20], which formally refer to the CDC 1994 criteria, but also recommend using a practical, clinical definition of CFS/ME in children with otherwise unexplained severe fatigue of more than three months duration. We cannot exclude the possibility that the relatively high incidence in children and adolescents may be partly due to the use of a less strict case definition of CFS/ME in young people. However, we find it unlikely that this potential over-reporting is substantial, as pediatricians probably are restrictive in using this diagnosis.

Some patients fulfilling the criteria for a diagnosis of CFS/ME may be missed in the current study due to the possible use of ICD-10 codes for other conditions with overlapping symptoms, such as neurasthenia, burn-out syndrome, malaise and fatigue, or fibromyalgia. However, while a diagnosis of G93.3 gives the right to social security benefits, such as sickness benefit or disability pension, this is most often not the case for, for example, neurasthenia, which includes many of the same symptoms but to a milder degree [2]. According to the guide from the Norwegian Directorate of Health, the code for neurasthenia should only be used when CFS/ME has been ruled out [2]. The ICD-10 guidelines also state that F48.0 ('neurasthenia') excludes G93.3 [21]. Thus, we regard G93.3 as the ICD-10 code most closely related to CFS/ME.

The incidence rates reported here are somewhat higher than the rates reported from the UK for the time period 1990 to 2001 [16], while the female to male ratios are comparable. Although the prognosis for an improvement in symptoms of CFS/ME is fairly good, full recovery seems rare [22]. The prognosis for children and adolescents seems to be better than for adults [23,24]. Due to the long duration of the disorder, our study estimating incidence rates is not directly comparable with previous prevalence surveys. However, the large sex difference reported here is in line with results from previous reports [1,8]. The previous prevalence studies are small with respect to the number of cases, and the scarce data available have usually limited analyses of sex and age distributions. For instance, from the UK, an overall prevalence of 0.30% for women and 0.09% for men and an estimated minimum yearly incidence at 15/100,000 has been reported [14]. This study was based on direct questioning of general practitioners combined with electronic database searches that covered 143,000 individuals 18- to 64-years old and included data from 122 cases only. Even stronger sex differences were reported from a US study based on medical record review following electronic searches in databases [15]. This latter study covered both primary and specialist health care and reported a prevalence of 0.12% for women and 0.02% for men, based on data from only 76 identified cases in total.

Survey-based approaches have also been utilized in several studies. In a telephone random-digit sampling study from the US, 43 cases were found among 56,146 participants [17]. The weighted prevalence estimates in that study were 0.37% for women and 0.08% for men. The study also reports the age distribution, but not for women and men separately. In a survey from Japan carried out among 1,430 participants in a health check-up program [11], the prevalence was estimated at 1.0%, based on 8 male and 6 female cases.

Although results from some questionnaire studies related to fatigue in general have been published from Denmark [25], Iceland [13] and Norway [26], only the Icelandic study attempts to report the prevalence of CFS/ME. In the study from Iceland, the sex distribution was similar to that in the current study, but the prevalence was higher (3.0% for women and 1.1% for men), based on a total of only 54 cases. In the Danish study, women had higher fatigue scores than men in a sample of 1,082 individuals responding to a questionnaire, and the variation in scores was also higher among women than among men, but CFS/ME cases were not defined [25]. The previous Norwegian study showed that the prevalence of general fatigue was high, with a slightly higher proportion of women than men with high scores on a fatigue questionnaire in a random population sample (N = 2,323) [26].

We observed a distinct age pattern in the incidence rate of CFS/ME, with the number of cases peaking in the age groups 10 to 19 years and 30 to 39 years. This pattern may suggest that development of CFS/ME might be caused by different etiological factors in different age groups, but could also be explained by increased vulnerability in these age groups. The female preponderance of CFS/ME indicates that sex hormones may play a part in the development of the condition. Puberty and the years after puberty are well-known vulnerable periods for the debut of several diseases, including autoimmune and psychiatric disorders [27]. Even though most women have not yet reached menopause in their late thirties, many women have given birth by this age. In pregnancy and postpartum periods, the risk of a wide range of conditions is increased due to rapid hormonal changes. For instance, migraine is a predominantly female disorder [28]. Menarche, menstruation, childbirth and menopause influence the frequency of migraine, and sex steroids are considered to play an important role [29]. Migraine is also highly prevalent in patients with CFS/ME [30]. Sex steroids cross the blood–brain barrier by passive diffusion and are also produced within the central nervous system [31]. These neurosteroids modulate brain networks and alter brain excitability [32]. Estrogen and progesterone are known to influence a range of neurotransmitters including serotonin, norepinephrine, dopamine and endorphins. Estrogen facilitates the glutamatergic system, potentially enhancing neuronal excitability, whereas progesterone activates GABAergic tone and suppresses neuronal reactivity. Changes in neurotransmitter systems can affect, for example, pain-processing networks, modulation of sensory input and cognition. Such mechanisms have been suggested to play a role in fibromyalgia [33] and may possibly also come into play in the development of CFS/ME.

Far more women than men are affected by multiple sclerosis (MS), and it has been suggested that the strong phenomenological, neurobehavioral and neuroimmune similarities between MS and CFS/ME indicate that CFS/ME is a neuroimmune disorder [34].

From the current results, one might hypothesize that hormonal changes increase the risk of CFS/ME in women. The pattern may also be compatible with the hypothesis of an infectious trigger for the condition. The age distribution observed in our study may be explained by primary exposure to an infectious agent in adolescents (first age peak) and subsequent reactivation of latent infection (second age peak). It has been shown that reactivation of latent (viral) infections may be triggered by stressful events, chronic stress or pregnancy [35].

Conclusions

In summary, in this large national study, we found that the CFS/ME risk is strongly dependent on sex and age. The distinctive sex and age patterns might be helpful when exploring potential causal mechanisms. Also, our findings indicate that clinicians should have a heightened awareness of the possibility of CFS/ME, especially in women in certain age groups presenting with symptoms of fatigue.

Abbreviations

CFS: chronic fatigue syndrome; CFS/ME: chronic fatigue syndrome/myalgic encephalomyelitis; CI: confidence interval; ICD-10: International Classification of Disease, version 10; ME: myalgic encephalomyelitis; MS: multiple sclerosis; NPR: Norwegian Patient Register.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SEH, LT, PM and CS conceived of the study. All authors were involved at all further stages of the study. IJB managed the data sets, carried out the statistical analyses and drafted the manuscript. NG and SG were particularly involved in the statistical analyses. KT and LT were particularly involved in the discussion of the findings and in shaping the conclusions. All authors commented and edited drafts of the manuscript, and read and approved the final manuscript.

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Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is associated with pandemic influenza infection, but not with an adjuvanted pandemic influenza vaccine

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ABSTRACT

Background: Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is associated to infections and it has been suggested that vaccination can trigger the disease. However, little is known about the specific association between clinically manifest influenza/influenza vaccine and CFS/ME. As part of a registry surveillance of adverse effects after mass vaccination in Norway during the 2009 influenza A (H1N1) pandemic, we had the opportunity to estimate and contrast the risk of CFS/ME after infection and vaccination.

Methods: Using the unique personal identification number assigned to everybody who is registered as resident in Norway, we followed the complete Norwegian population as of October 1, 2009, through national registries of vaccination, communicable diseases, primary health, and specialist health care until December 31, 2012. Hazard ratios (HRs) of CFS/ME, as diagnosed in the specialist health care services (diagnostic code G93.3 in the International Classification of Diseases, Version 10), after influenza infection and/or vaccination were estimated using Cox proportional-hazards regression.

Results: The incidence rate of CFS/ME was 2.08 per 100,000 person-months at risk. The adjusted HR of CFS/ME after pandemic vaccination was 0.97 (95% confidence interval [CI]: 0.91–1.04), while it was 2.04 (95% CI: 1.78–2.33) after being diagnosed with influenza infection during the peak pandemic period.

Conclusions: Pandemic influenza A (H1N1) infection was associated with a more than two-fold increased risk of CFS/ME. We found no indication of increased risk of CFS/ME after vaccination. Our findings are consistent with a model whereby symptomatic infection, rather than antigenic stimulation may trigger CFS/ME.

1. Introduction

Mass vaccination, as done in several countries during the novel influenza A (H1N1) pandemic in 2009, is a public health action where the benefit is assumed to outweigh the risk of adverse events. Surveillance of adverse reactions is needed for an appraisal of the balance between benefit and risk, and to ensure both appropriate use of vaccines and public confidence in vaccine safety. After 2009, narcolepsy and Guillain–Barré syndrome have been linked to H1N1 vaccines, although the final verdicts concerning causality have not yet been made [1–6]. The two diseases are considered to be autoimmune, possibly triggered by infection or immunization [7–10].

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a debilitating disorder, characterized by severe fatigue of unknown cause. In addition to fatigue, CFS/ME is associated with a wide range of symptoms, including post-exertional malaise, pain, unrefreshing sleep, and cognitive impairment [11]. Alterations in both the innate and acquired immune systems have been reported [12–17]. Disease clustering and even small epidemics have been described [18–24]. It has been proposed that autoimmune mechanisms may play a role [25–27], and that, in addition to infections, immunizations could be involved in the onset or continuation of the pathophysiological process.

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In the fall of 2009, a decision was made to offer vaccination, free of charge, to all citizens in Norway, using an H1N1 vaccine with an AS03 adjuvant. Utilizing nationwide registries, a surveillance program to monitor effects and side effects of vaccination was established [28]. Although many influenza infections may be asymptomatic, and only a proportion of symptomatic subjects will seek health care, a sufficient number of subjects with influenza infections were included in Norwegian primary care and communicable disease registries in the peak pandemic period October–December 2009, to provide an opportunity to prospectively estimate and compare effects of vaccination and influenza infection on the risk of CFS/ME.

2. Methods

In Norway, a few cases of novel influenza A (H1N1) infection were registered from July 2009, but the majority of laboratory-confirmed cases were noted in a peak period from October 1 through December 31, 2009 [28]. In October 2009, two vaccines became available: Pandemrix (GlaxoSmithKline), containing the squalene-based adjuvant AS03, and Celvapan (Baxter), which did not. The vaccinations coincided with the peak time period of the pandemic wave.

The study population of this nationwide cohort study is the resident population on October 1, 2009, as registered in the Norwegian population registry [29] (n = 4840,084). Data from the Norwegian Immunization Registry [30], the reimbursement data from primary care physicians, the Norwegian Surveillance System for Communicable Diseases [31], and the national specialist health care register (Norwegian Patient Register—NPR) were linked to the study base using the unique 11-digit personal identification number provided to all residents. Subjects with missing or invalid information in the population registry (n = 7873), subjects who had received a diagnosis of CFS/ME prior to October 1, 2009, as registered in the NPR (n = 1951), subjects who had been vaccinated with Celvapan but not with Pandemrix (n = 481), and subjects who were vaccinated but who lacked registration of the date of vaccination (n = 2573), were excluded. In total, 4827,209 subjects were eligible for the present study. This registry-based study was approved by the Regional Committee for Medical and Health Research Ethics for South-Eastern Norway (reference number: 2010/2583).

The vaccination registry provided information on the two influenza vaccines against the A(H1N1)pdm09 strain used in Norway. One dose of Pandemrix was recommended by the Norwegian Institute of Public Health. Vaccinations were offered from October 19, 2009, and all vaccinations from this date until the early months of 2010 were included in the analyses.

Information on infection with the H1N1 influenza virus was obtained from two different sources. One source was from consultations in primary health care and emergency outpatient clinics, where all consultations must be reported to obtain reimbursement. Diagnoses are reported with codes from the International Classification of Primary Care, Second Edition (ICPC-2). The code for influenza-like illness (R80) was taken as a measure of H1N1 infection when the diagnosis was made during the pandemic peak period (October 1 through December 31, 2009). We considered R80 codes outside this period as insufficiently specific to be used as evidence for exposure to H1N1, as other infections may have caused similar symptoms. The other source of information on influenza infection was registrations in the Norwegian Surveillance System for Communicable Diseases of a confirmed antigenic test for H1N1 as reported from microbiology laboratories. The majority of these infections were reported during the peak period. However, due to the high specificity of these tests, reports from outside the peak period were included.

Table 1
Characteristics of subjects with follow-up time* (n = 4822,337), all residents of Norway as of October 1, 2009.

	n	%
Year of birth		
<1940	518,118	10.7
1940–1949	503,836	10.4
1950–1959	612,885	12.7
1960–1969	698,012	14.5
1970–1979	672,069	13.9
1980–1989	604,677	12.5
1990–1999	634,351	13.1
2000–2009	583,261	12.1
Sex		
Male	2410,311	49.9
Female	2416,898	50.1
Vaccinated with Pandemrix		
No	2931,549	60.7
Yes, during peak period*	1841,982	38.2
Yes, other time period	53,678	1.1
Influenza diagnosis in primary care in peak period		
No	4713,230	97.6
Yes	113,979	2.4
Laboratory-confirmed influenza		
No	4814,155	99.7
Yes, during peak period	10,582	0.2
Yes, other time period	2472	0.1

* Exclusions: 7873 subjects with missing or invalid status in the population register; 481 subjects who were vaccinated with Celvapan but not with Pandemrix; 2573 subjects with missing date of first vaccination with Pandemrix; 1951 subjects who had been diagnosed with CFS/ME prior to October 1, 2009.

The specialist health care register (NPR) includes diagnostic information (International Classification of Diseases, Version 10—ICD-10) for outpatient consultations and hospitalizations in the specialized health services. All cases of CFS/ME (ICD-10 code G93.3) were included. In addition, the population registry provided information about potential confounders, such as sex and year of birth. Year of birth was categorized into 10-year groups, with all persons born prior to 1960 merged into one group.

Crude incidence rates were estimated as the number of new cases of CFS/ME divided by the sum of person-months at risk, both overall and by exposure. Hazard ratios (HRs) of CFS/ME, with associated 95% confidence intervals (CIs), were estimated using Cox proportional-hazards regression, with number of whole months since the start of the study (October 1, 2009) as the time metric. Subjects were followed until diagnosis of CFS/ME, death, emigration, or end of the study (December 31, 2012), whichever occurred first. By default, observations from 4872 subjects with zero follow-up time (due to emigration, death, or diagnosis of CFS/ME in October 2009) were excluded, leaving 4822,337 subjects in the analysis. Indicator variables of vaccination (yes/no) and influenza infection (yes/no) were included as time-varying covariates. Subjects were considered as being exposed to vaccination from the month of first vaccination with Pandemrix and as exposed to infection from the month of first influenza diagnosis. The infection and vaccination exposure status persisted until the end of follow-up. Data were analyzed using the Stata 13 software (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.).

3. Results

From November 1, 2009 through 2012, 3737 new cases of CFS/ME were registered in the specialist health care register. Among these, 138 were registered in November and December 2009, 1092 in 2010, 1258 in 2011, and 1249 in 2012. Nearly 40% were vaccinated with Pandemrix (Table 1). More than 97% of these vaccinations were given during the peak pandemic period. Table 1

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Table 2
Incidence rates and hazard ratios (HRs) of CFS/ME, with associated 95% confidence intervals (CIs), according to pandemic vaccination and influenza infection. Follow-up time from October 1, 2009, through December 31, 2012 for 4822,377 residents of Norway born 1899–2009.

Year of birth		No. of person-months at risk	No. of cases	Incidence rate*	Crude	Adjusted**	
					HR	HR	95% CI
1899–2009	*Influenza*						
	Yes	4422,760	227	5.13	2.55	2.04	1.78–2.33
	No	175,460,422	3510	2.00	1.0	1.0	
	Vaccinated						
	Yes	69,375,157	1408	2.03	0.95	0.97	0.91–1.04
	No	110,508,025	2329	2.11	1.0	1.0	
1899–1979	*Influenza*						
	Yes	2033,877	94	4.62	2.49	1.65	1.34–2.03
	No	109,159,893	2020	1.85	1.0	1.0	
	Vaccinated						
	Yes	42,335,444	781	1.84	0.95	0.89	0.82–0.98
	No	68,858,326	1333	1.94	1.0	1.0	
1980–2009	*Influenza*						
	Yes	2388,883	133	5.57	2.46	2.45	2.05–2.92
	No	66,300,529	1490	2.25	1.0	1.0	
	Vaccinated						
	Yes	27,039,713	627	2.32	0.94	1.08	0.98–1.20
	No	41,649,699	996	2.39	1.0	1.0	

* Number of new cases per 100,000 person-months at risk.
** Stratified Cox analysis with separate baseline hazards functions for each year-of-birth category and adjusted for sex and the other variable in the table.

Table 3
Incidence rates and hazards ratios (HRs) of CFS/ME, with associated 95% confidence intervals (CIs), according to exposure to pandemic vaccination and influenza infection. Follow-up time from October 1, 2009, through December 31, 2012, for 4822,377 residents of Norway born 1899–2009.

		No. of person-months at risk	No. of cases	Incidence rate*	Adjusted**	
Vaccinated	Infected				HR	95% CI
No	No	107,475,182	2165	2.01	1.0	
Yes	No	67,985,240	1345	1.98	0.98	0.91–1.05
No	Yes	3032,843	164	5.41	2.08	1.78–2.44
Yes	Yes	1,389,917	63	4.53	1.88	1.46–2.42

* Number of new cases per 100,000 person-months at risk.
** Stratified Cox analysis with separate baseline hazards functions for each year-of-birth category and adjusted for sex.

shows that 2.4% of the population was registered with an influenza infection in primary health care consultations, while only about 0.3% had a verified antigenic diagnosis from a microbiology laboratory.

Among eligible subjects for follow-up (n = 4822,337), the crude incidence rate of CFS/ME was 2.08 per 100,000 person-months (3737 cases and 179,883,182 person-months). The adjusted HR of CFS/ME after influenza infection was 2.04 (95% CI: 1.78–2.33), while it was 0.97 (95% CI: 0.91–1.04) after vaccination (Table 2). The HR of CFS/ME after influenza infection was higher for subjects who were below 30 years of age in 2009 (born in 1980–2009, lower part of Table 2) compared to older subjects. The same pattern of associations between CFS/ME and the two exposures was found when the regression analysis was performed separately for males and females (results not shown). Table 3 shows the joint effects of influenza infection and vaccination. In the absence of influenza infection, the incidence rates were about the same for vaccinated and unvaccinated subjects. The rates were increased for infected subjects, independent of vaccination status.

4. Discussion

This study shows that CFS/ME occurring after the influenza A (H1N1) pandemic was associated with a diagnosis of influenza-like illness. We found no evidence of an association between pandemic influenza vaccination and CFS/ME. This suggests that development of CFS/ME may be a reaction to fever, malaise, and general activation of the immune system, rather than the more restricted antigenic stimulation from a vaccine.

An advantage of this study is that the whole nation formed the cohort, reducing the potential for selection bias. Another advantage is that the registration of exposures (vaccination and infection) was made before and independently of the registration of the endpoint (CFS/ME). A limitation of registry data is that the classifications of exposures and the disease outcomes are not designed for research purposes. There is some degree of misclassification of the variables. During the pandemic, a web-based, electronic reporting form for registration of influenza vaccinations into the immunization registry was set up. A comparison between the number of vaccines distributed to local communities and the number of registered vaccinations indicates that as many as 200,000 subjects (about 4% of the population) could have been vaccinated without registration [32].

CFS/ME is a heterogeneous disorder and different case definitions have been used [11]. The diagnosis of CFS/ME is based on the presence of a constellation of subjective symptoms, obtained through patient interviews as well as the exclusion of other conditions that may result in chronic fatigue. There are no objective signs or biomarkers for this disease. It is a weakness of registry data that diagnoses are not based on strict criteria from a research protocol. We did not perform in-depth case validation as part of this study.

The registrations of influenza from primary health care were restricted to the peak pandemic period in Norway. We assume that the majority of subjects with influenza-like symptoms who received an R80 code in the period October–December 2009 were infected with the H1N1 influenza virus rather than another respiratory pathogen. No other influenza virus was known to be circulating in the population at this time. The reporting of diagnoses from

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primary health care consultations is believed to be complete as it is required for reimbursements from the government. However, many patients with influenza symptoms will not seek medical care during an influenza season. Only 2.4% of the study population received a physician diagnosis of influenza during the peak pandemic period. Presumably, patients with more severe symptoms seek medical care. The proportion of the population with clinical influenza infection during the pandemic has been estimated to be 20–30% [33,34], implying that a substantial number of the subjects categorized as uninfected in this study, actually were infected and therefore misclassified. Non-differential misclassification of exposures and end-points in a prospective study usually leads to underestimation of the effect of the exposure on the outcome, in this case influenza infection on later CFS/ME occurrence, suggesting that the true relative risk may be higher than estimated by us.

In Norway, two distinct age peaks in the incidence of CFS/ME have been reported. The first peak is in the age group 10 to 19 years, and the second peak is in the age group 30 to 39 years [35]. In the present study, a slightly stronger effect of influenza infection was found for subjects below the age of 30 years, as compared to subjects aged 30 years or older. However, the possibility that this difference may be due to illness behavior (the proportion of ill persons who seek medical care) should be kept open.

There is still a lack of large, well-characterized cohort studies with CFS/ME as endpoint. Studies in general practice suggest that prolonged fatigue is not specifically related to features of common viral illnesses [36,37]. By following subjects with either acute Epstein–Barr virus infection, Q fever or Ross river virus infection in a rural region of Australia, it was found that 11% had prolonged illness with disabling fatigue [20]. A cohort of subjects with infectious mononucleosis (IM), influenza or tonsillitis, but without a comparison group free of infections, found the odds of clinically diagnosed fatigue to be 4.4 times higher when IM was compared to influenza and 6.6 times higher when IM was compared to tonsillitis [38]. Our finding of a significantly increased risk of CFS/ME in the general population after influenza infection is novel and needs confirmation. Fatigue was found to be frequent in the weeks after having suffered from the Asian influenza during the winter of 1957–58 [39], and a case report of CFS/ME after the recent pandemic has been published [40], but we are not aware of other population-based studies.

It is reassuring that no evidence for increased risk of CFS/ME was found among vaccinated subjects. Studies of the effect of influenza vaccination on immune function in subjects with CFS/ME have not suggested excess early reactions or altered antibody responses [41–43]. Also an earlier Norwegian study showed no relation between vaccination against meningococcal disease and CFS/ME [44].

5. Conclusions

In conclusion, pandemic influenza vaccination in a mass campaign does not increase the risk of CFS/ME. The findings suggest that clinically manifest influenza-like illness may play a causal role for the development of at least a proportion of cases of this disorder.

Conflict of interest statement

None.

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Enheten för läkemedelssäkerhet registrerar och hanterar inkomna rapporter om misstänkta biverkningar på samma sätt oavsett vilket läkemedel det handlar om. Vi mottar rapporter både från hälso- och sjukvårdpersonal samt från konsumenter/patienter. Vid behov frågas också efter uppföljande information. Alla rapporter om allvarliga misstänkta biverkningar skickas från det svenska systemet vidare till EudraVigilance enligt gällande regelverk.

Totalt (vid sökning 2015-10-27) har vi fått in 800 rapporter om misstänkta biverkningar på Gardasil samt 3 rapporter om misstänkta biverkningar på Cervarix. Flest antal rapporter har kommit in under 2012. Däremot kan vi förstås inte ange vad totala antalet kommer att bli under innevarande år.
När det gäller diagnosen POTS, inkom en rapport under 2013. Sedan har vi erhållit ytterligare 4 rapporter och dessa har kommit under de senaste månaderna i år (från i somras).
Vad gäller övriga symptom; svimning, yrsel, trötthet så förefaller störst antal rapporter ha kommit in under 2012. Detta ser också ut att vara fallet för artralgi.
Som bilaga medföljer våra sökningar, där också söktermer finns angivna.

Vid behov, så står vi gärna till tjänst med ytterligare upplysningar

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Totalt 803 rapporter

Rapporturval :
Biverkningsrapporter inkomna till Läkemedelsverket mellan år 1965 och år 2015

Valda ATC-koder :
J07BM02; J07BM01

Valda produkter :
Gardasil ;Gardasil;Cervarix

Valda reaktioner som MedDRA PT :
Ingen begränsning

Valda kroppssystem som MedDRA SOC :
Ingen begränsning

Valda rapportörstyper :
Ingen begränsning

Utdrag ur Läkemedelsverkets databas BiSi

Ingående läkemedel

Totalt 803 rapporter

ATC	Ingående läkemedel	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totalt
J07BM01	Gardasil	18	46	34	11	16	312	159	94	110	800
J07BM02	Cervarix					1	2				3
	Totalt	**18**	**46**	**34**	**11**	**17**	**314**	**159**	**94**	**110**	**803**

Datauttag utfört 2015-10-27

Totalt 277 rapporter

Rapporturval :
Senaste uppgifterna inkom begränsat till mellan 1965-01-01 och 2015-10-27

Valda ATC-koder :
J07BM01; J07BM02

Valda produkter :
Valda produkter :Cervarix; Gardasil ; Gardasil

Valda reaktioner som MedDRA PT :
Post viral fatigue syndrome; Chronic fatigue syndrome; Fatigue; Dizziness; Dizziness postural; Dizziness exertional; Procedural dizziness; Vertigo; Vertigo positional; Vertigo labyrinthine; Vertigo CNS origin; Cervicogenic vertigo; Postural orthostatic tachycardia syndrome; Arthralgia; Presyncope; Psychogenic pseudosyncope; Syncope

Valda kroppssystem som MedDRA SOC :
Ingen begränsning

Utdrag ur Läkemedelsverkets databas BiSi

Reaktioner som MedDRA-lista SOC, PT per år

Totalt 277 rapporter

ATC	Ingående läkemedel	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totalt
J07BM01	Gardasil	2	10	5	3	5	111	56	35	50	277
	Totalt	**2**	**10**	**5**	**3**	**5**	**111**	**56**	**35**	**50**	**277**

SOC	Reaktioner MedDRA PT	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totalt
Card	Postural orthostatic tachycardia syndrome							1		4	5
Totalt	**Rapporter**							**1**		**4**	**5**
Ear	Vertigo						2				2
Totalt	**Rapporter**						**2**				**2**
Genrl	Chronic fatigue syndrome								1	2	3
	Fatigue		1	2		1	46	30	15	17	112
Totalt	**Rapporter**		**1**	**2**		**1**	**46**	**30**	**16**	**19**	**115**
Infec	Post viral fatigue syndrome							1	1		2
Totalt	**Rapporter**							**1**	**1**		**2**
Musc	Arthralgia		1	2			7	5		3	18
Totalt	**Rapporter**		**1**	**2**			**7**	**5**		**3**	**18**
Nerv	Dizziness		6	1	3	2	59	22	14	20	127
	Dizziness postural								1		1
	Presyncope						1				1
	Syncope	2	2	1		2	22	13	16	23	81
Totalt	**Rapporter**	**2**	**8**	**2**	**3**	**4**	**79**	**31**	**25**	**37**	**191**

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