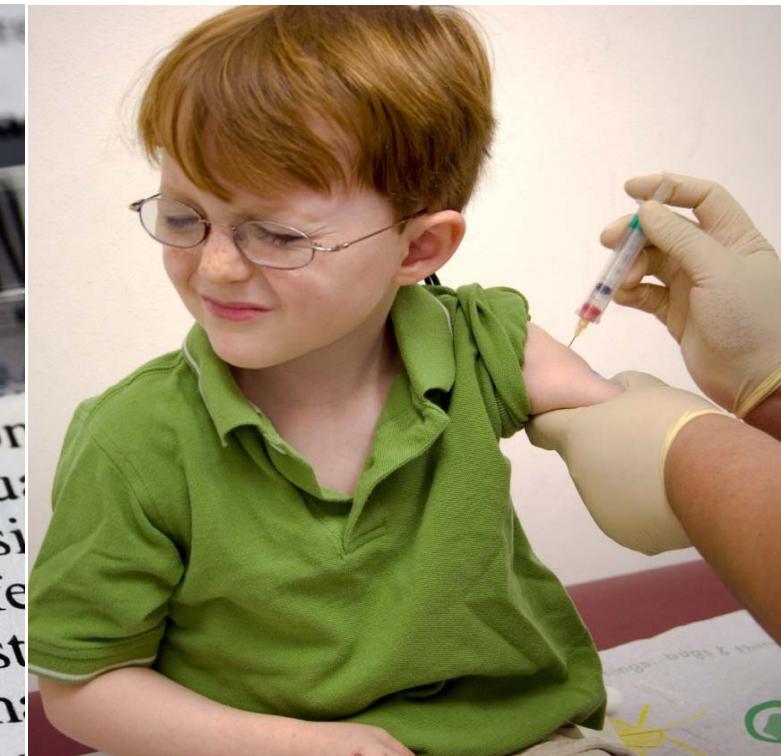
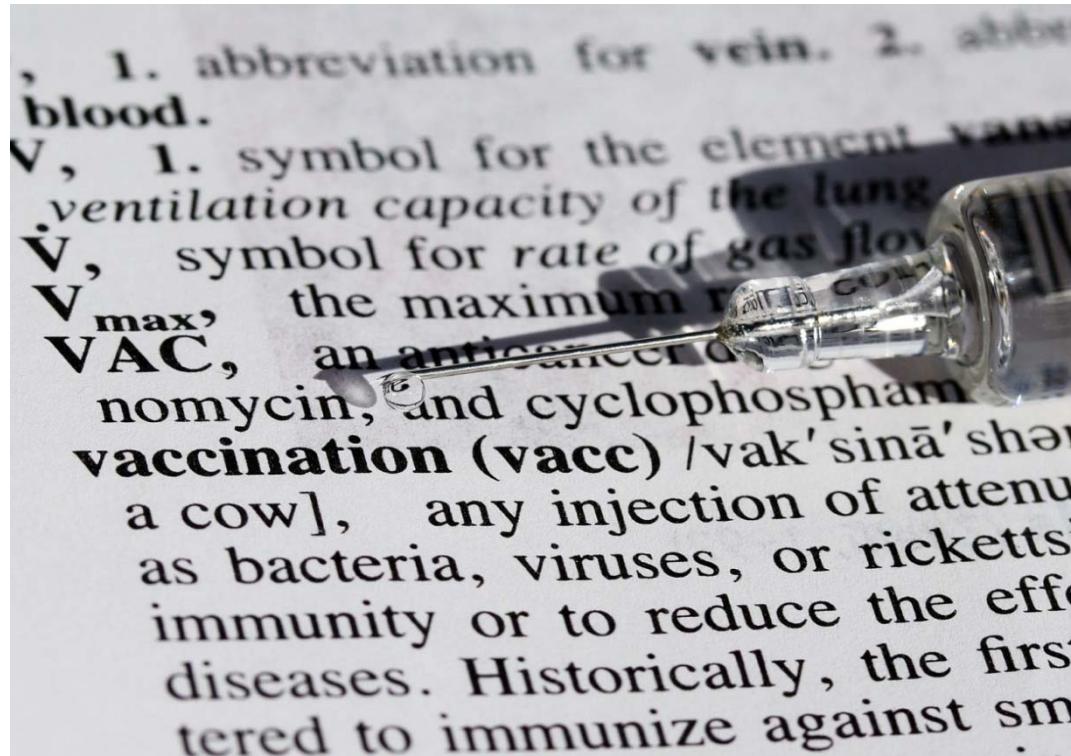


BEWAKING VAN DE VACCINVEILIGHEID IN BELGIË: PLAATS EN BEPERKINGEN VAN EEN BENADERING GEBASEERD OP ACHTERGRONDINCIDENTIES





Het Federaal Kenniscentrum voor de Gezondheidszorg

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BEWAKING VAN DE VACCINVEILIGHEID IN BELGIË: PLAATS EN BEPERKINGEN VAN EEN BENADERING GEBASEERD OP ACHTERGRONDINCIDENTIES

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COLOFON

Titel:	Bewaking van de vaccinveiligheid in België: plaats en beperkingen van een benadering gebaseerd op achtergrondincidenties
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Externe Validatoren:	Jean-Michel Dogné (Université de Namur), Wilson Kumanan (Ottawa Hospital Research Institute), Béatrice Swennen (ULB)
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Layout:	Ine Verhulst
Disclaimer:	<ul style="list-style-type: none">De externe experten werden geraadpleegd over een (preliminaire) versie van het wetenschappelijke rapport. Hun opmerkingen werden tijdens vergaderingen besproken. Zij zijn geen coauteur van het wetenschappelijke rapport en gingen niet noodzakelijk akkoord met de inhoud ervan.Vervolgens werd een (finale) versie aan de validatoren voorgelegd. De validatie van het rapport volgt uit een consensus of een meerderheidsstem tussen de validatoren. Zij zijn geen coauteur van het wetenschappelijke rapport en gingen niet noodzakelijk alle drie akkoord met de inhoud ervan.Tot slot werd dit rapport unaniem goedgekeurd door de Raad van Bestuur.Alleen het KCE is verantwoordelijk voor de eventuele resterende vergissingen of onvolledigheden alsook voor de aanbevelingen aan de overheid.
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■ VOORWOORD

Het menselijke brein is niet zo sterk in het omgaan met probabiliteiten. Zeker niet als het om zeldzame of extreem zeldzame verschijnselen gaat, zo leren ons de studies van psychologen. Of het nu om een kans van één op vijfduizend gaat, of één op vijfhonderdduizend, het maakt niet zoveel verschil: van zodra we ons min of meer levendig kunnen voorstellen hoe het zou zijn als het ons overkwam, gaan we de waarschijnlijkheid grof overschatte. Zeker wanneer het gaat om een of andere calamiteit die we ten allen prijzen willen vermijden. Van dat laatste maakt de verzekeringssector overigens gretig gebruik.

Sommige preventiemaatregelen blijken hiervoor bijzonder gevoelig te zijn, met de vaccinaties als frappant voorbeeld. Bij elke (nieuwe) vaccinatiecampagne duiken wel ergens sterk gemediatiseerde 'slachtoffers' van het vaccin op, met vaak vrij drastische gevolgen op de uiteindelijke dekkingsgraad van het vaccin. Het heeft geen zin op de pianist te schieten – de media volgen in deze hun eigen logica. Evenmin moet men ten strijde trekken tegen sommige uitwassen waarbij heuse complottheorieën worden verzonden. De overheid heeft gewoon de plicht om – wanneer zij een preventieve maatregel ondersteunt – ook alle mogelijke garanties te bieden dat dit geen onredelijke risico's inhoudt, en dat de voordelen ruim opwegen tegen de potentiële nadelen of complicaties.

Eigenlijk heb je hier drie elementen voor nodig: (1) je moet kunnen detecteren wanneer bepaalde problemen abnormaal frequent worden. Daarvoor moet je (2) weten wat de normale frequentie (de *background rate* in het jargon) is in een niet aan het vaccin blootgestelde bevolking. En (3) uiteraard moet je ook weten wie blootgesteld is. Gemakkelijker gezegd dan gedaan, want het gaat om zeldzame verschijnselen.

De specifieke vraag die ons vanuit het Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten werd gesteld is om na te gaan in hoeverre België een adequaat antwoord heeft op de tweede uitdaging, namelijk het berekenen van achtergrondcijfers. Kan een klein land als België hier überhaupt zinvolle cijfers bekomen, of moeten we radicaal de Europese kaart trekken. De antwoorden zijn wat genuanceerder. Het laatste woord is hiermee zeker niet gezegd, maar wij hopen toch een steentje bij te kunnen dragen in deze maatschappelijk belangrijke kwestie.

Raf MERTENS
Algemeen Directeur



■ SAMENVATTING

INLEIDING

Toezicht op de veiligheid van vaccinatie betreft het opsporen, evalueren, verwerven van inzicht in en het voorkomen van ongewenste effecten die kunnen optreden na vaccinatie (OENV). De rol van een programma dat de veiligheid bewaakt, bestaat erin veiligheidssignalen te vergaren die na een doorgedreven evaluatie postvaccinale ongewenste verschijnselen (PVOV) aan het licht brengen die eerder niet werden geïdentificeerd, niet werden herkend of onvoldoende werden begrepen. Het basisprincipe bij het detecteren van veiligheidssignalen bestaat in het analyseren van de Geobserveerde/Verwachte (O/E) verschijnselen: het aantal geobserveerde ongewenste verschijnselen binnen de gevaccineerde groep wordt vergeleken met wat te verwachten valt mocht er geen vaccinatie hebben plaatsgevonden. Ligt het percentage complicaties bij personen die het vaccin kregen beduidend hoger dan verwacht, dan wordt een veiligheidssignaal gegenereerd dat vervolgens verder op het bestaan van een oorzakelijk verband moet worden geanalyseerd. Er bestaan verschillende methodes om het verwachte aantal adverse events na vaccinatie te berekenen. Een daarvan bestaat erin het incidentiepercentage van een bepaalde aandoening binnen de globale populatie te extrapoleren tot de gevaccineerde populatie, d.i. de achtergrondincidentie.

Dit rapport evalueert de relevantie en haalbaarheid van de achtergrondincidentiebenadering voor toezicht op de veiligheid van immunisatie in België. De voornaamste onderzoeksvraag die ons hier dan ook bezig houdt is: in hoe verre is het haalbaar om de achtergrondincidentie van ongewenste effecten te berekenen en te gebruiken om de veiligheid van vaccinatie op grote schaal binnen België te evalueren?

We beginnen ons antwoord op die vraag met een overzicht van de diverse beschikbare databronnen in België die informatie bevatten over de achtergrondincidentie van een reeks aandoeningen en vatten hun mogelijkheden en beperkingen samen. Dan zullen we bij wijze van proef trachten de achtergrondincidentie van een aantal aandoeningen in België te ramen. Tot slot beschrijven we de bewaking van de vaccinatieveiligheid in België en zoomen we in op de moeilijkheden en op de mogelijke ruimte voor verbetering.

DATABASES DIE GEGEVENS OVER DE ACHTERGRONDINCIDENTIE IN BELGIË KUNNEN VERSTREKKEN

Administratieve gegevensbronnen

In het raam van hun financiering maken de ziekenhuizen Minimaal Klinische Gegevens (MKG) - Minimaal Ziekenhuisgegevens (MZG) over aan de Federale Overheidsdienst (FOD) Volksgezondheid (FOD VG). Die gegevens zouden kunnen worden gebruikt om de achtergrondincidentie te berekenen. Niettemin vertonen ze een aantal beperkingen. Eerst en vooral bevatten deze MKG geen informatie over ambulante zorg, wat ertoe leidt dat ziekte-episoden die niet tot een opname hebben geleid niet worden gedetecteerd. Anderzijds laten ze geen onderscheid toe tussen een eerste en vervolgopnames voor dezelfde ziekte-episode. Ten derde zou een verschijnsel dat wordt aangeduid als "DRG creep", m.a.w. het systematisch en weloverwogen overwaarderen van de case mix om een hogere financiering voor het ziekenhuis te bekomen, kunnen leiden tot een systematische fout bij het evalueren van de achtergrondincidentie van bepaalde aandoeningen, zoals in België reeds werd aangetoond voor thrombocytopenie.¹ Ten vierde en hoewel de gegevens in theorie om de 6 maanden worden overgemaakt, bedraagt de achterstand in de verwerking momenteel om en bij de 2 jaar. Ten vijfde: de exacte leeftijd van de patiënt is niet gekend, wel zijn of haar geboortejaar; dat maakt het bijzonder moeilijk om de achtergrondincidentie binnen de meest gevaccineerde leeftijdsgroep, namelijk jonge kinderen, te berekenen. Tot slot wordt de diagnose niet ingevoerd door de behandelende klinische medicus, en wordt die zoals dit voor de meeste administratieve databases geldt, evenmin gecontroleerd, noch gevalideerd.

CARENET is een beveiligd internetplatform voor de uitwisseling tussen ziekenhuizen en ziekteverzekeringsinstellingen van informatie over afzonderlijke ziekenhuisopnames: tijdstip van opname, verblijfsduur, diagnose en medische procedures die door het RIZIV worden terugbetaald. Het voornaamste doel van CARENET is die gegevensoverdracht eenvoudiger en sneller te laten verlopen. CARENET zou dus sneller dan MKG toegang kunnen bieden tot gegevens over

specifieke ziekten. Niettemin moeten we aanstippen dat het veld voor de diagnose een alfanumeriek veld is, waarin met andere woorden vrije tekst of ICD-9-CM codes kunnen worden ingevoerd. Uit interviews van strategische zegslieden bleek dat de validiteit van de data van de verschillende ziekenhuizen heel sterk kan verschillen. Sommige ziekenhuizen werken met professionele codeurs die voor het invoeren van de gegevens dezelfde ICD-9-CM als de MKG-database hanteren. Andere ziekenhuizen laten dit veld dan weer invullen door niet nader omschreven klinische medewerkers die doorgaans voor vrije tekst opteren. In dat geval moeten er text mining technieken aan te pas komen om de gegevens te extraheren en te analyseren. We dienen ook aan te stippen dat alleen het invullen van het diagnoseveld wettelijk verplicht is; dat in dat veld accurate en begrijpelijke gegevens moeten voorkomen, staat nergens; evenmin bestaat er enige kwaliteitscontrole ten aanzien van de diagnose. Een van de gemeenschappelijke kenmerken van CARENET en MKG is dat ze zich momenteel beperken tot gegevens van gehospitaliseerde patiënten.

Voor ieder sterfgeval stelt een arts een overlijdensakte op en worden de doodsoorzaak (oorzaken) vermeld. Voor ieder sterfgeval stellen de internationale regels van de WGO en de ICD-10 codes een reeks diagnoses voor: oorspronkelijke doodsoorzaak (voornaamste), rechtstreekse, onrechtstreekse en verbonden oorzaken.

Sentinel netwerken

In België zijn er 2 Sentinel netwerken voor huisartsen actief. Het eerste bestaat sinds 1978 en wordt georganiseerd door het WIV en telt vandaag zowat 200 huisartsen, goed voor ongeveer 1,8% van alle Belgische huisartsen. Dit Sentinel netwerk is een heel betrouwbaar toezichtsysteem gebleken voor een hele reeks epidemiologische gegevens met betrekking tot de gezondheid, waaronder diabetes, hersenbloedingen, kanker, ongevallen; toch werden tot dusver slechts weinig gegevens die in verband worden gebracht met OENV verzameld. De lijst met gecontroleerde aandoeningen wordt ieder jaar herbekeken; op vraag van de overheid kunnen potentiële veiligheidsverschijnselen aan de lijst worden toegevoegd.

Anderzijds is er Intego, een netwerk van vrijwillige Sentinel huisartsen in Vlaanderen (1,05% van de huisartsen in 55 praktijken) dat door het Academisch Centrum Huisartsgeneeskunde van de Katholieke Universiteit



Leuven wordt gecoördineerd. De incidentie wordt op een website volgens ICPC2 code (International Classification of Primary Care) per jaar en per leeftijdsgroep gepubliceerd.

Beide Sentinel netwerken vertonen een aantal beperkingen. Eerst en vooral is de betrokken populatie niet heel nauwkeurig gekend, waardoor er geen uitsluitsel kan worden gegeven over de precisie bij de verwerking van de achtergrondincidentie. Bovendien is de populatie van de Sentinel netwerken relatief beperkt en alvast niet toereikend om stabiele berekeningen toe te laten van de achtergrondincidentie voor verschijnselen die zich behoorlijk zeldzaam voordoen. Een derde belangrijke beperking is dat deze netwerken zich beperken tot informatie van huisartspraktijken, en dus geen ziekenhuiscijfers bevatten. Dit probleem kan deels worden ondervangen mochten de zorgverstrekkers binnen ziekenhuizen die de patiënten onder hun hoede hebben, systematisch feedback bezorgen aan de huisartsen; in hoeverre dit zou bijdragen tot betrouwbare berekeningen is niet heel duidelijk.

Pedisurv (Pediatric diseases Surveillance) werd in 2002 opgericht door het WIV en is een surveillancenetwerk van Belgische kinderartsen (n=504; 35% van alle pediatres) en Brussels huisartsen (n=354; 36% van de huisartsen in Brussel). Dit netwerk legt zich toe op de studie van zeldzame infectieziekten bij kinderen en controleert de impact van maatregelen van gezondheidszorg, zoals vaccinatie, binnen deze groep. Tot op heden werd nog geen enkele OENV in de lijst opgenomen. Pedisurv is theoretisch gezien wel in staat om zeldzame en ernstige onbedoelde ongewenste verschijnselen te monitoren; de mogelijkheid om intussuscepties op te nemen werd recent besproken. Wat de toegankelijkheid van de gegevens betreft, kunnen de Pedisurv gegevens bij het WIV worden opgevraagd, maar daarvoor moet vooraf een overeenkomst worden ondertekend. De jaarverslagen zijn algemeen toegankelijk op <https://www.wiv-isb.be/pedisurv/>.

BEREKENING VAN DE ACHTERGRONDINCIDENTIE: EEN PILOTSTUDIE

We hebben getracht om de incidentie te ramen van een aantal aandoeningen die zou kunnen dienen als achtergrondincidentie, teneinde de haalbaarheid van het proces te beoordelen en de mogelijke problemen en scheeftrekkingen te onderzoeken. We hebben deze pilotstudie toegespitst op drie ernstige potentiële PVOV, m.a.w. wiegendoor, Syndroom van Guillain-Barré en stuipen.

We hebben aangetoond dat het voor een aantal aandoeningen mogelijk is om de achtergrondincidentie te produceren die redelijk overeenstemmen met de cijfers die in andere landen werden geobserveerd. Aan de volledigheid van het overlijdensregister hoeft er niet te worden getwijfeld; anderzijds zal de diagnose "wiegendoor" geleidelijk accurater kunnen worden gesteld, aangezien de wet van 2003 autopsie verplicht bij alle gevallen van wiegendoor van kinderen <18 maanden. Ook de berekening van de achtergrondincidentie uitgaande van het MKG-bestand bleek in sommige gevallen goed mogelijk; voorwaarde was wel dat die gegevens betrekking hadden op een nauwkeurig gedefinieerde aandoening die altijd tot een ziekenhuisopname leidt, zoals het syndroom van Guillain-Barré; bijkomende voorwaarde is dat enkel de hoofddiagnose als uitgangspunt wordt gebruikt. Toch dient het MKG-bestand niet in de eerste plaats epidemiologische doelen.

TOEZICHT OP DE VACCINVEILIGHEID IN BELGIË

De geneesmiddelenbewaking in België valt onder de wettelijke verantwoordelijkheid van de divisie geneesmiddelenbewaking van het FAGG, een agentschap dat ressorteert onder de FOD Volksgezondheid. Mocht de benadering via de achtergrondincidentie worden geïmplementeerd, dan zou de bevoegdheid voor het bepalen van het geobserveerde aantal PVOV bij het FAGG liggen.

Het FAGG ontvangt individuele rapporten van beoefenaars van de gezondheidszorg (artsen, apothekers, tandartsen) en rapporten van individuele cases van houders van vergunningen voor het in de handel brengen (HVH), m.a.w. farmaceutische bedrijven. De HVH die door beoefenaars van de gezondheidszorg, of door onderzoekers van klinische proeven, of nog, via wetenschappelijke publicaties op de hoogte worden gebracht van ernstige bijwerkingen, moeten die binnen de 15 dagen vanaf ontvangst van de informatie aan het FAGG melden. Ook promotoren van klinische tests moeten alle Vermoedens van Onverwachte Ernstige Bijwerkingen (SUSAR - Suspected Unexpected Serious Adverse Reaction) die tijdens hun klinische test optraden melden en dit zowel voor geneesmiddelen met een vergunning voor het in de handel brengen als die zonder die vergunning. Sinds kort worden nog andere bronnen van individuele rapporten aangeboord:

- Sinds juli 2012 kunnen ook individuen PVOV rechtstreeks aan het FAGG melden.
- Ook via Vaccinet, een online systeem voor het bestellen van alle vaccins in Vlaanderen dat sinds 2004 operationeel is, kunnen intussen gegevens over vermoedelijke bijwerkingen worden ingevoerd; in hoeverre die optie tegenwoordig al wordt gebruikt, is nog niet geweten.

We onderzochten de vaccingegevens die het FAGG sinds 2008 vergaarde. Tabel 1 toont het aantal vermoedens van PVOV dat jaarlijks aan het FAGG werd gemeld (de gegevens voor het jaar 2012 dekken enkel de eerste helft van het jaar). Jaarlijks worden zowat 200 rapporten overgemaakt. De piek die in 2009 werd vastgesteld, is hoofdzakelijk het gevolg van de rapportering van bijwerkingen van het vaccin Pandemrix dat tijdens de influenza-epidemie werd gebruikt. Het aantal meldingen is, zoals u merkt, uiterst laag, te meer daar het de meldingen van ongewenste verschijnselen voor alle in België gebruikte vaccins betreft.

Tabel 1 – Aantal vermoedens van postvaccinale bijwerkingen die tussen 2008 en medio 2012 aan het FAGG werden gemeld

Jaar	Aantal
2008	216
2009	352
2010	170
2011	208
2012	85
Totaal	1031



BESPREKING EN CONCLUSIE

We hebben aangetoond dat de achtergrondincidentie van een aantal ziektes in België kan worden berekend. Hoewel de betrouwbaarheid van die achtergrondincidentie niet met zekerheid kan worden bevestigd, wordt vermoed dat die behoorlijk hoog is voor de incidentie uitgaande van de hoofddiagnose of voor duidelijk gedefinieerde aandoeningen die een systematische ziekenhuisopname vergen, of voor de doodsoorzaken die op de overlijdensakten staan vermeld. Het actuele Belgische systeem voor datavergaring is te sterk gefragmenteerd om een betrouwbare achtergrondincidentie te bepalen voor andere ziektes.

België is echter niet in staat om alle uitdagingen die een doelmatig gebruik van de achtergrondincidentie in de weg staan het hoofd te bieden, ook al kan er een redelijk betrouwbare achtergrondincidentie worden geproduceerd. Het onderrapporteren van ongewenste verschijnselen aan de bevoegde overheid en de relatief kleine populatie van vaccinrecipiënten in België vormen twee belangrijke uitdagingen. De laatste uitdaging kan niet worden opgelost en wijst op de nood aan een systeem van veiligheidsbewaking op Europees niveau. Die bewaking op Europees niveau ontwikkelt zich snel.

Als we deze elementen in aanmerking nemen lijkt het niet gepast om te investeren in de ontwikkeling van een benadering volgens de achtergrondincidentie voor de bewaking van vaccinveiligheid in België. Dat betekent echter niet dat de bewaking van de vaccinveiligheid in een impasse zit. Het is van cruciaal belang dat de meldingen van PVOV aan het FAGG worden verbeterd. De rechtstreekse melding van PVOV door consumenten, wat binnenkort wordt geïmplementeerd, zou een belangrijke stap in die richting kunnen betekenen. Anderzijds moet ook worden gestreefd naar een beter meldgedrag bij de verstrekkers van gezondheidszorgen en naar een meer gestandaardiseerde classificatie van PVOV. Om op gepaste wijze te kunnen communiceren over risico's en de risico's maximaal te beperken is er ook een snellere analyse en interpretatie van mogelijke veiligheidssignalen geformuleerd door EMA of andere bronnen noodzakelijk.

De mogelijkheid om alternatieve strategieën van bewaking van vaccinveiligheid in België te implementeren, viel buiten de reikwijdte van dit project. Dergelijke strategieën moeten uitgaan van een algemene beoordeling van de nood aan informatie in het kader van gezondheidszorg in België en moeten uitpakken met een globaal plan voor datavergaring en gegevensanalyse. Merk op dat EMA de techniek van data mining reeds toepast op EudraVigilance, een bestand dat veiligheidsmeldingen aan het FAGG bevat. Ook cohortenstudies en reeksen zelfgecontroleerde cases zouden kunnen worden geïmplementeerd via het IMA-bestand (InterMutualistisch Agentschap) dat zowel gegevens bevat over bepaalde vaccinatietypes als over ziekenhuisopname, overlijden en het gebruik van specifieke diensten van de gezondheidszorg of geneesmiddelen. De haalbaarheid van dergelijke benadering moet verder worden geëvalueerd.



■ AANBEVELINGEN^a

Aan de Minister van Volksgezondheid en het FAGG:

- Gezien de tekortkomingen van de beschikbare gegevensbronnen in ons land en de beperkte omvang van de bevolking, raden we niet aan om te investeren in een systematische detectie van veiligheidssignalen op basis van de achtergrondincidentie.
- Deze signaaldetectie moet bij voorkeur gebeuren in een Europees kader (via het Europese Geneesmiddelenagentschap), en België moet hiertoe bijdragen door gegevens aan te leveren over potentiële ongewenste verschijnselen. We bevelen dus aan om op nationaal niveau maatregelen te treffen om de meldingen door professionele zorgverleners en door de consumenten van mogelijke postvaccinale ongewenste verschijnselen (PVOV) te verbeteren; het nieuwe internetplatform voor het melden van ongewenste verschijnselen aan het FAGG vormt een prima insteek om vooruitgang op dit vlak te boeken. Deze maatregelen zouden moeten gebaseerd zijn op een analyse van de barrières in verband met het rapporteren van bijwerkingen in België.
- Naast het detecteren van signalen, zou het evenwel nuttig kunnen zijn om de achtergrondincidentie van een beperkt aantal ernstige verschijnselen te berekenen met het oog op risicocommunicatie op nationaal niveau, in het geval er grote ongerustheid zou optreden in de algemene bevolking over de veiligheid van vaccins. Dat zou het geval kunnen zijn voor wiegendood of voor ernstige invaliderende ziektes zoals het syndroom van Guillain-Barré.
- Men zou ook andere, niet in deze studie behandelde benaderingen kunnen verkennen om het verband tussen vaccins en bepaalde ongewenste verschijnselen na te gaan, zoals het gebruik van prospectieve cohorten aan de hand van bestaande databases (bv. terugbetelingsgegevens).

Onderzoeksagenda:

- Er moet worden onderzocht wat de haalbaarheid is van andere technieken voor het detecteren van veiligheidssignalen in België die efficiënter en krachtiger zijn dan de analyse van de geobserveerde vs. de verwachte ratio die in dit rapport werd behandeld. Met die technieken bedoelen we onder meer case-control studies of nog de analyse van reeksen zelfgecontroleerde cases.

^a Alleen het KCE is verantwoordelijk voor de aanbevelingen aan de overheid



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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ACIP	Advisory Committee on Immunization Practices
ADROI	Adverse Drug Reactions On-line Information Tracking
AE	Adverse event
AEFI	Adverse effect following immunization
AFP	Acute flaccid paralysis
ARIMA	Autoregressive integrated moving average
ASR	Annual Safety Report
BC	Brighton collaboration
BCCD	Brighton collaboration case definitions
BCPH	Belgian Centre for Pharmacovigilance for medicines for Human use
BIFAP	“Base de datos para la investigación farmacoepidemiológica en atención primaria” (Database for Pharmacoepidemiological Research in Primary Care)
BR	Background rate
CBIP/BCFI	Centre Belge d'Information Pharmacothérapeutique / Belgisch Centrum voor Farmacotherapeutische Informatie
CDC	Centre for Disease Control and Prevention
CI	Confidence interval
CIDP	Chronic inflammatory demyelinating polyneuropathy
CIOMS	Council for International Organizations of Medical Sciences
DRG	Diagnosis Related Group
E	Expected number of the adverse event in the vaccinated population
EBGM	Empirical Bayes geometric mean
ECDC	European Centre for Disease Control and Prevention
ECHIM	European Community Health Indicators Monitoring
EISN	European Influenza Surveillance Network
EMA	European Medicines Agency
eRMR	Electronic Reaction Monitoring Reports
ESI	Events of specific interest



F	Female
FAMHP	Federal Agency for Medicines and Health Products (L'Agence Fédérale des Médicaments et des Produits de Santé / Federaal Agentschap voor geneesmiddelen en gezondheidsproducten)
FDA	US Food and Drug Administration
FPS (SPF / FOD)	Federal Public Service (Service Publique Fédéral / Federale Overheidsdienst)
GBS	Guillain-Barré Syndrome
GP	General Practitioner
GPRD	General Practice Research Database
HBR	Hospital Billing Records
HCR	Hospital Clinical Records
HDD	Hospital discharge diagnoses
HIC	Health insurance companies
IC	Information component
ICD	International Classification of Diseases
ICPC	International Classification of Primary Care
ICSR	Individual case safety reports
ID	Identification
Ig	Immunoglobulins
IKAROS	GelIntegreerd Kind Activiteiten Regio OndersteuningsSysteem
IPD	Invasive pneumococcal diseases
IPH (ISP / WIV)	Institute of Public Health (Institut Scientifique de Santé Publique / Wetenschappelijk Instituut Volksgezondheid)
LoS	Length of stay
M	Male
MAH	Marketing authorization holders
maxSPRT	Maximised sequential probability ratio test
MCD (MKG-MZG / RCM-RHM)	Minimal Clinical Data (Minimaal Klinische Data - Minimaal Ziekenhuis data / Résumé Clinique Minimum – Résumé Hospitalier Minimum)



MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products regulatory Agency
MIO	Million
MMN	Multifocal motor neuropathy
NIHDI (INAMI / RIZIV)	National Institute for Health and Disability Insurance (Institut national d'assurance maladie-invalidité / Rijksinstituut voor ziekte- en invaliditeitsverzekering)
NINCDS	National Institutes of Neurological and Communicative Disorders and Stroke
O	Observed number of the adverse event in the vaccinated population
OE	Observed-to-expected ratio
ONE	Office de la Naissance et de l'Enfance
Pedisurv	Pediatric Diseases Surveillance
PP	Practice population
PRR	Proportional Reporting Ratio
PPS	Prospective Payment System
PPV	Positive predictive value
PSUR	Periodic Safety Update Report
RCD	READ Code classification
ROR	Reporting odds ratio
SCD	Sudden Cardiac Death
SD	Sudden Death
SID	Sudden infant deaths
SIR	Standardized Incidence Ratio
SMT	Safety Management Team
SPC	Summary of Product Characteristics
SPE	Studycentre for Perinatal Epidemiology
SPMA	Standardized Procedures for Mortality Analysis
SSF	Special Solidarity Fund
SUD	Sudden unexplained/unexpected deaths
SUDI	Sudden Unexpected Death in Infancy



SUSAR	Suspected Unexpected Serious Adverse Reactions
UMLS	Unified Medical Language System
US	United States
VAERS	Vaccine Adverse Event Report System
VAESCO	Vaccine Adverse Event Surveillance & Communication
VSD	Vaccine Safety Datalink
WHO	World Health Organization
YCG	Yearly contact group



■ SYNTHESE

1 INLEIDING

Het bewaken van de postvaccinale veiligheid betreft het opsporen, evalueren, verwerven van inzicht in en het voorkomen van postvaccinale ongewenste verschijnselen (PVOV). De rol van een programma dat de veiligheid bewaakt, bestaat erin veiligheidssignalen te vergaren die na een doorgedreven evaluatie PVOV aan het licht brengen die eerder niet werden geïdentificeerd, niet werden herkend of onvoldoende werden begrepen. Dit kan het geval zijn voor PVOV met een dermate lage frequentie dat ze tijdens studies voorafgaand aan de goedkeuring door de mazen van het net glipten, omdat de steekproef te beperkt was. PVOV kunnen ook een gevolg zijn van eerder niet-gegemerkte farmacologische effecten van het vaccin, interacties met andere geneesmiddelen of vaccins, factoren die verband houden met specifieke patiëntenpopulaties, individuele patiëntenfactoren (zoals farmacogenomische factoren). Ziekte-episoden en vaccinatie kunnen ook coïncidenteel optreden, waarbij er geen causaal verband tussen beide verschijnselen bestaat.

Een foutieve interpretatie van ongewenste gevolgen voor de gezondheid die slechts een tijdelijk verband met de vaccinatie vertonen, kan grote onrust onder de bevolking over de veiligheid van vaccins wekken en het algemeen vertrouwen in vaccinatieprogramma's schaden. Voor de volksgezondheid is het dan ook cruciaal dat de vaccinatieveiligheid wordt bewaakt. Dat laat enerzijds toe de balans tussen risico's en baten van de vaccinatie te controleren zodat er kan worden bijgestuurd wanneer die balans niet langer gunstig blijkt te zijn. Anderzijds biedt bewaking een objectieve basis om zowel de bevolking als de artsen gerust te stellen wanneer publicaties over coïncidentele associaties met ziekten bezorgdheid wekken.



1.1 Verschillende benaderingen van signaaldetectie

De veiligheid kan zowel passief, als actief, maar ook passief en actief worden bewaakt, al naargelang de wijze waarop de informatie wordt vergaard. Passieve bewaking gaat uit van spontane meldingen van ongewenste verschijnselen, terwijl actieve bewaking doelgericht informatie over vaccinaties en ongewenste verschijnselen vergaart. Het principe van detectie van veiligheidssignalen loopt bij beide vormen van bewaking echter sterk gelijk: het aantal ongewenste verschijnselen binnen de gevaccineerde groep wordt vergeleken met wat te verwachten valt als er geen vaccinatie had plaatsgevonden. Ligt het percentage ongewenste verschijnselen bij personen die het vaccin kregen beduidend hoger dan verwacht, dan wordt een veiligheidssignaal gegenereerd. De verdere analyse van dat signaal moet uitmaken of er sprake is van causaliteit. Het verwachte aantal postvaccinale ongewenste verschijnselen kan volgens verschillende methodes worden berekend. Een daarvan bestaat erin de incidentie van een bepaalde aandoening binnen de globale populatie te extrapoleren naar de gevaccineerde populatie, d.i. de achtergrondincidentie. Het geobserveerde aantal ongewenste verschijnselen (O) binnen de gevaccineerde populatie wordt vervolgens vergeleken met het verwachte aantal (E). Een O/E -ratio die beduidend hoger ligt dan één, vormt een veiligheidssignaal. Dit is de zogenaamde benadering volgens de achtergrondincidentie, die in dit rapport centraal staat. Andere methodes voor het detecteren van veiligheidssignalen zijn onder andere data mining en cohortenstudies.

1.2 Doel van de studie

Dit rapport gaat de relevantie en haalbaarheid na van een benadering volgens de achtergrondincidentie voor het bewaken van de vaccinatieveiligheid in België. Omdat het Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG) wordt geconfronteerd met meldingen van postvaccinale ongewenste verschijnselen die reëel of artefacten kunnen zijn, maakte het FAGG deze vraag over aan het KCE. Ongeacht of die verschijnselen al dan niet reëel zijn, moet het Agentschap bij vaccinatieprogramma's snel tot de gepaste actie en tot risicocommunicatie kunnen overgaan. België kent momenteel geen actieve bewaking van de vaccinatieveiligheid en grijpt maar heel sporadisch terug naar methodes van data mining. De benadering die uitgaat van achtergrondincidentie zou op dit vlak dus een centrale rol naar zich kunnen toetrekken. België beschikt echter tot op heden nauwelijks over enige achtergrondgegevens. De voornaamste onderzoeksvergadering die ons hier dan ook bezig houdt, is na te gaan in hoeverre de berekening en het gebruik van de achtergrondincidentie van ongewenste effecten voor het evalueren van veiligheidsproblemen bij vaccinatie op grote schaal in België haalbaar zijn.

We beginnen ons antwoord op die vraag met een overzicht van de diverse databronnen die in België beschikbaar zijn en die informatie over de achtergrondincidentie van een reeks aandoeningen bevatten. Aan het einde vatten we hun mogelijkheden en beperkingen samen. Dan zullen we bij wijze van proef trachten de achtergrondincidentie van een aantal aandoeningen in België te berekenen. Tot slot beschrijven we de bewaking van de vaccinatieveiligheid in België en zoomen we in op de moeilijkheden en op de mogelijke ruimte voor verbetering.

2 DATABASES DIE GEGEVENS OVER DE ACHTERGRONDINCIDENTIE IN BELGIË KUNNEN VERSTREKKEN

2.1 Gegevensbronnen van de overheid

2.1.1 *Minimale Klinische Gegevens*

In het raam van hun financiering maken de ziekenhuizen Minimale Klinische Gegevens (MKG) - Minimale Ziekenhuisgegevens (MZG) over aan de Federale Overheidsdienst (FOD) Volksgezondheid (FOD VG). Het MKG-bestand bevat een samenvatting van ieder ziekenhuisverblijf: demografische gegevens over de patiënt, administratieve gegevens over de specifieke verblijfsdata en diagnosegegevens met een onbeperkt aantal ICD-9-CM codes. Die gegevens kunnen dienen als basis voor de berekening van de achtergrondincidentie. Niettemin vertonen ze een aantal beperkingen. Eerst en vooral bevatten deze MKG geen informatie over ambulante zorg, wat ertoe leidt dat ziekte-episoden die niet tot een opname hebben geleid, niet worden gedetecteerd. Anderzijds laten ze geen onderscheid toe tussen een eerste en vervolgopnames voor dezelfde ziekte-episode. Ten derde zou een verschijnsel dat wordt aangeduid als "DRG creep", m.a.w. het systematisch en weloverwogen overwaarderen van de case mix om een hogere financiering voor het ziekenhuis te bekomen, kunnen leiden tot een systematische fout bij het evalueren van de achtergrondincidentie van bepaalde aandoeningen, zoals in België reeds werd aangetoond voor thrombocytopenie. Ten vierde en hoewel de gegevens in theorie om de 6 maanden worden overgemaakt, bedraagt de achterstand in de verwerking momenteel om en bij de 2 jaar. Ten vijfde: de exacte leeftijd van de patiënt is niet gekend, wel zijn of haar geboortejaar; dat maakt het bijzonder moeilijk om de achtergrondincidentie binnen de meest gevaccineerde leeftijdsgroep, namelijk jonge kinderen, te berekenen. Tot slot wordt de diagnose niet ingevoerd door de behandelende klinische medicus, en wordt die zoals dit voor de meeste administratieve databases geldt, evenmin gecontroleerd, noch gevalideerd.

2.1.2 *CARENET*

CARENET is een beveiligd internetplatform voor de uitwisseling tussen ziekenhuizen en ziekteverzekeringsinstellingen van informatie over afzonderlijke ziekenhuisopnames: tijdstip van opname, verblijfsduur, diagnose en medische procedures die door het RIZIV worden terugbetaald. Het voornaamste doel van CARENET is die gegevensoverdracht eenvoudiger en sneller te laten verlopen. CARENET zou dus sneller dan MKG toegang kunnen bieden tot gegevens over specifieke ziekten. Niettemin moeten we aanstippen dat het veld voor de diagnose een alfanumeriek veld is, waarin met andere woorden vrije tekst of ICD-9-CM codes kunnen worden ingevoerd. Uit interviews van strategische zegslieden bleek dat de validiteit van de data van de verschillende ziekenhuizen heel sterk kan verschillen. Sommige ziekenhuizen werken met professionele codeurs die voor het invoeren van de gegevens dezelfde ICD-9-CM als de MKG-database hanteren. Andere ziekenhuizen laten dit veld dan weer invullen door niet nader omschreven klinische medewerkers die doorgaans voor vrije tekst opteren. In dat geval moeten er text mining technieken aan te pas komen om de gegevens te extraheren en te analyseren. We dienen ook aan te stippen dat alleen het invullen van het diagnoseveld wettelijk verplicht is; dat in dat veld accurate en begrijpelijke gegevens moeten voorkomen, staat nergens; evenmin bestaat er enige kwaliteitscontrole ten aanzien van de diagnose. Een van de gemeenschappelijke kenmerken van CARENET en MKG is dat ze zich momenteel beperken tot gegevens van gehospitaliseerde patiënten.



2.1.3 Overlijdensregister

Voor ieder sterfgeval in België stelt een arts een overlijdensakte op; ook de doodsoorzaak (doodsoorzaken) wordt (worden) geregistreerd. Voor ieder sterfgeval kunnen een aantal diagnoses worden ingevoerd, vastgelegd door de internationale regels van de WGO en de ICD-10 codes: oorspronkelijke doodsoorzaak (voornaamste), rechtstreekse, onrechtstreekse en verbonden oorzaken. De gegevens over de doodsoorzaken kunnen bij iedere Gemeenschap worden opgevraagd; daarvoor moet wel een overeenkomst worden ondertekend. Afhankelijk van de Gemeenschappen hadden de gegevens over de doodsoorzaak die in juni 2012 beschikbaar waren, betrekking op overlijdens in 2009 of 2010 (achterstand van 1-2 jaar). Het Vlaamse Gewest publiceert ook onbewerkte gegevens op zijn website. Verder zijn er ook nationale gegevens beschikbaar, vb. op de website van de FOD Economie (<http://statbel.fgov.be/en/statistics/figures/>) of op de site van het WIV (<https://www.wiv-isb.be/epidemio/spma/>), weliswaar met een grotere achterstand (zowat 3 jaar). De meest recente gegevens die in september 2012 beschikbaar waren, hadden betrekking op 2008. De beperkingen van deze database werden niet onderzocht. Niettemin blijkt uit de vergaarde gegevens dat de regio's verschillende praktijken hanteren voor het invoeren van plotse overlijdens.

Supranationaal is er Euro-MOMO (monitoring van mortaliteit). Dit door de EU gefinancierd project ging in 2008 van start en wordt door het Deense Statens Serum Institut gecoördineerd. Euro-MOMO doet in 20 EU-landen, waaronder België, aan mortaliteitsmonitoring zonder onderscheid te maken naar de doodsoorzaak (onbewerkte gegevens). Doel van dit project is de oversterfte in Europa door influenza en andere mogelijke bedreigingen van de volksgezondheid in reële tijd te controleren.

2.2 Sentinelnetwerken

2.2.1 Netwerken voor huisartsen

In België zijn er 2 sentinelnetwerken voor huisartsen actief. Het eerste bestaat sinds 1978 en wordt georganiseerd door het Wetenschappelijk Instituut van Volksgezondheid (WIV) en telt vandaag zowat 200 huisartsen, goed voor ongeveer 1,8% van alle Belgische huisartsen. Dit sentinelnetwerk is een bijzonder betrouwbaar systeem gebleken voor de bewaking van een hele reeks epidemiologische gegevens met betrekking tot de gezondheid, waaronder diabetes, hersenbloedingen, kanker, ongevallen; toch werden tot dusver slechts weinig gegevens die verband houden met PVOV verzameld. De lijst met gecontroleerde aandoeningen wordt ieder jaar herbekeken; op vraag van de overheid kunnen potentiële veiligheidsverschijnselen aan de lijst worden toegevoegd.

Anderzijds is er Intego, een netwerk van vrijwillige sentinelhuisartsen in Vlaanderen (1,05% van de huisartsen in 55 praktijken) dat door het Academisch Centrum Huisartsgeneeskunde van de Katholieke Universiteit Leuven wordt gecoördineerd. De incidentie wordt op een website gepubliceerd volgens ICPC2^a code per jaar en per leeftijdsgroep.

Beide sentinelnetwerken kunnen nuttig zijn voor de berekening van de achtergrondincidentie. Niettemin vertonen ook zij een aantal beperkingen. Eerst en vooral is de betrokken populatie niet heel nauwkeurig gekend, waardoor er geen uitsluitsel kan worden gegeven over de precisie bij de berekening van de achtergrondincidentie. Bovendien is de populatie van de sentinelnetwerken relatief beperkt en alvast niet toereikend om stabiele berekeningen toe te laten van de achtergrondincidentie voor verschijnselen die zich behoorlijk zeldzaam voordoen. Een derde belangrijke beperking is dat deze netwerken zich beperken tot informatie van huisartspraktijken, en dus geen ziekenhuiscijfers bevatten. Dit probleem kan deels worden ondervangen mochten de zorgverstrekkers binnen ziekenhuizen die de patiënten onder hun hoede hebben, systematisch feedback bezorgen aan de huisartsen; in hoeverre dit zou bijdragen tot betrouwbare cijfers is niet heel duidelijk.

^a International Classification of Primary Care



2.2.2 Pedisurv

PediSurv (Pediatric diseases Surveillance) werd in 2002 opgericht door het WIV en is een surveillancenetwerk van Belgische kinderartsen ($n=504$; 35% van alle pediatres) en Brusselse huisartsen ($n=354$; 36% van de huisartsen in Brussel). Dit netwerk legt zich toe op de studie van zeldzame infectieziekten bij kinderen en controleert de impact van maatregelen van gezondheidszorg, zoals vaccinatie, binnen deze groep. Het surveillancesysteem is vrijwillig, maar de deelnemers worden verzocht om zich maandelijks te melden ook al deden er zich geen specifieke gevallen voor. Per case moet een formulier worden ingevuld met alle demografische en klinische gegevens en met de vaccinatiestatus. De sensitiviteit van de PediSurv bewaking (m.a.w. het aantal gevallen dat via het bewakingssysteem werd gedetecteerd) werd via een capture-recapture onderzoek (met 3 verschillende bronnen) voor invasieve pneumokokkenziekte in 2005-06 geraamd op 73%. PediSurv bewaakt in 2012 de volgende ziekten: mazelen, rubella, bof, invasieve pneumokokkenziekte, acute slappe verlamming, congenitaal rubellasyndroom en het hemolytisch-uremisch syndroom. De lijst van bewaakte aandoeningen wordt ieder jaar door een Stuurgroep opnieuw geëvalueerd en overeenkomstig de vereisten inzake gezondheidszorg bijgewerkt. Bij de opname op de lijst van nieuwe ziekten wordt ook de werklast van de klinische medici die de gegevens rapporteren in aanmerking genomen. Tot op heden werd nog geen enkele PVOV op de lijst opgenomen. PediSurv is theoretisch gezien wel in staat om zeldzame en ernstige onbedoelde ongewenste verschijnselen te monitoren; de mogelijkheid om intussuscepties op te nemen werd recent besproken. Wat de toegankelijkheid van de gegevens betreft, kunnen de PediSurv gegevens bij het WIV worden opgevraagd, maar daarvoor moet vooraf een overeenkomst worden ondertekend. De jaarverslagen zijn algemeen toegankelijk op <https://www.wiv-isb.be/pedisurv/>.

3 BEREKENING VAN DE ACHTERGRONDINCIDENTIE: EEN PILOTSTUDIE

We hebben getracht om de incidentie te berekenen van een aantal aandoeningen die zou kunnen dienen als achtergrondincidentie, teneinde de haalbaarheid van het proces te beoordelen en de mogelijke problemen en systematische fouten te onderzoeken. We hebben deze pilotstudie toegespitst op drie ernstige potentiële PVOV, m.a.w. wiegendoorzaak, Syndroom van Guillain-Barré en stuipen.

3.1 Wiegendoorzaak

In de geïndustrialiseerde wereld vormt wiegendoorzaak (WD) de hoofdoorzaak voor sterfte bij kinderen tussen 1 en 11 maanden. De achtergrondincidentie van wiegendoorzaak is cruciaal om de veiligheid van het vaccin na de commercialisering te evalueren omdat de eerste immunisatieprogramma's van jonge kinderen in de tijd samenvallen met de piekleeftijd van de wiegendoorzaakincidentie. Voor onze benadering gebruikten we de overlijdensregisters als gegevensbron (van het Vlaams Agentschap Zorg en Gezondheid, Fédération de Wallonie-Bruxelles en het Brussels Hoofdstedelijk Gewest).



Tabel 1 – Wiegendood (ICD10* code R95 als initiële doodsoorzaak) in België volgens overlijdensaktes, 2000-2009

Populatie / jaar	Gemiddeld aantal per jaar 2000-09	Gemiddeld cijfer per jaar per 1000 levende geboortes 2000-09	Cijfer van 2009 per 1000 levende geboortes	globaal % met autopsie*
Vlaanderen	26,1	0,41	0,29	60%
Brussel	6,5	0,42	0,33	59%
Wallonië	23,0	0,59	0,47	59%
België	55,6	0,47	0,35	59%
Overige gebrekkig omschreven en niet-gespecificeerde doodsoorzaken	1,6	0,01	0,01	80%

* autopsie op het ogenblik van de codering van het overlijden in uitvoering of gepland ICD

ICD10: International Classification of Diseases versie 10

Bronnen: Vlaams Agentschap Zorg en Gezondheid, Fédération de Wallonie-Bruxelles en het Brussels Hoofdstedelijk Gewest

De cijfers berekend op basis van de Belgische overlijdensakten zijn vergelijkbaar met de nationale overlijdensstatistieken in andere EU-landen. De aangetroffen regionale verschillen (de cijfers in Wallonië zijn hoger) worden verklaard door verschillen in codering, maar de patronen zijn zowel in tijd als naar leeftijd identiek). De voorbije jaren vertonen de cijfers een dalende trend, terwijl het aantal autopsies sinds de invoering van de nieuwe wet toeneemt; die wet bepaalt dat de diagnose van wiegendood via een autopsie moet worden gesteld. De Belgische data over doodsoorzaken lijken geschikt om de achtergrondincidentie van wiegendood in België te berekenen. Gezien de in de tijd dalende trend

moeten we de meest recente gegevens gebruiken; die zijn op regionaal niveau beschikbaar met een vertraging van 1 tot 2 jaar.

3.2 Syndroom van Guillain-Barré

Het Syndroom van Guillain-Barré (SGB) is een acute demyeliniserende aandoening van de perifere zenuwen. Wat de onderliggende etiologie is van de ziekte, is nog niet precies gekend. Gedacht wordt echter dat de ziekte een immunologische oorzaak heeft en door een acute infectie wordt uitgelokt. Andere mogelijke oorzaak zijn vaccins; zo werden er al associaties tussen vaccins en SGB gemeld, hoewel de onderliggende mechanismen nog niet zijn opgehelderd. Dat er bij de controle van de vaccinveiligheid dan ook aandacht moet worden besteed aan SGB, hoeft niet te verwonderen. We gebruiken het bestand van de MKG.

In de periode 2004-09 werden gemiddeld 550 met SGB gerelateerde ziekenhuisopnames gemeld (met SGB als primaire of secundaire diagnose); voor 55% van deze opnames gold SGB als hoofddiagnose. In 25% van alle SGB-gerelateerde opnames en in 18% van de opnames met SGB als hoofddiagnose werden dubbele opnames geregistreerd (doorverwijzing naar een ander ziekenhuis of heropname van de patiënt). Laten we de heropnames buiten beschouwing, dan varieert het bruto cijfer voor SGB als hoofddiagnose van 2,2 tot 2,4 per 100 000 en voor SGB als een van de diagnoses van 3,9-5,0 per 100 000. De bruto cijfers voor SGB als hoofddiagnose blijven voor de betreffende jaren stabiel. Het cijfer van de ziekenhuisopname neemt toe naarmate de leeftijd stijgt.

De Belgische gegevens van gehospitaliseerde patiënten die in de MKG werden opgenomen met SGB als hoofddiagnose liggen iets hoger dan de achtergrondincidentie van SGB die de literatuur meldt voor West-Europese landen, maar de diagnoses zijn niet gevalideerd. Andere studies toonden aan dat - niet gevalideerde - cijfers uitgaande van de gegevens van patiënten die uit het ziekenhuis werden ontslagen - de werkelijke SGB-cijfers overschatte; reden daarvoor is dat andere diagnoses niet uit deze cijfers werden geweerd. Een verkeerde classificatie van chronische neurologische aandoeningen bij de eerste opname, en de terugbetalingsvoorschriften voor immunoglobulinen kunnen verantwoordelijk zijn voor een inflatie van het aantal opnames dat in België als SGB wordt gecodeerd. Vermits de diagnose bij postvaccinale ongewenste verschijnselen (of "geobserveerde verschijnselen") doorgaans

wordt geëvalueerd en gecontroleerd, zal de berekende SGB-achtergrondincidentie uitgaande van de, regelmatig bijgewerkte, literatuur, waarschijnlijk een beter en meer robuust beeld geven dan de niet-gevalideerde MKG. Toch kunnen de "geobserveerde" SGB-manifestaties die niet (of nog niet) zijn gevalideerd, worden getoetst aan de achtergrondincidentie berekend op basis van de Belgische MKG-informatie.

Dit voorbeeld toont ook aan dat het tellen van alle voorvallen van een bepaalde aandoening in MKG zonder onderscheid naar primaire en secundaire diagnose leidt tot een aanzienlijke overschatting van de achtergrondincidentie. Het zou dan ook verstandig zijn om voor de telling enkel de voorvallen met SGB als primaire diagnose in aanmerking te nemen, hoewel we met dergelijke strategie het aantal niet-gedetecteerde gevallen niet kunnen ramen.

3.3 Stuipen

De incidentie hiervan in Intego bedraagt in de periode van 2008 - 2010 voor meisjes jonger dan vijf jaar 92/100 000 personen per jaar en voor jongens uit dezelfde leeftijdscategorie 99/100 000; de incidentie voor alle leeftijdsgroepen bedraagt 9/100 000 voor vrouwen en 14/100 000 voor mannen. Die cijfers liggen lager dan wat er in de literatuur wordt gemeld, wat wellicht verband houdt met het feit dat de huisarts in België niet wordt geraadpleegd voor stuipen; dat leidt tot een onderschatting.

De incidentie van stuipen gestandaardiseerd volgens leeftijd en berekend op basis van de ziekenhuisgegevens (MKG-bestand) varieert van 120/100 000 personen per jaar in 2004 tot 112/100 000 in 2009. Die cijfers zijn vergelijkbaar met wat op Europees niveau werd geobserveerd (VAESCO project). We stippen aan dat een toename door vaccinatie moeilijk te detecteren valt als we uitgaan van alle stuipen; stuipen die in verband worden gebracht met vaccinatie gaan hoogstwaarschijnlijk gepaard met koorts en die vertegenwoordigen slechts een klein aandeel van alle gemelde stuipen. Die ramingen kunnen in ieder geval niet rechtstreeks worden vergeleken met ramingen uit de literatuur, vermits het type stuipen en de vergaringsmethodes te sterk verschillen.

3.4 Haalbaarheid en betrouwbaarheid van de berekening van de achtergrondincidentie in België

We hebben aangetoond dat we voor een aantal aandoeningen de achtergrondincidentie kunnen produceren die redelijk overeenstemt met de cijfers die in andere landen werden geobserveerd. Aan de volledigheid van het **overlijdensregister** hoeft er niet te worden getwijfeld; anderzijds zal de diagnose "wiegendood" geleidelijk accurater kunnen worden gesteld, aangezien de wet van 2003 autopsie verplicht bij alle gevallen van wiegendood van kinderen <18 maanden. Ook de berekening van de achtergrondincidentie uitgaande van het MKG-bestand bleek goed mogelijk, ondanks de beperkingen die we in hoofdstuk 2.1.1 bespraken; die gegevens moeten dan wel betrekking hebben op een nauwkeurig gedefinieerde aandoening die altijd tot een ziekenhuisopname leidt, zoals het syndroom van Guillain-Barré; bijkomende voorwaarde is dat enkel de hoofddiagnose als uitgangspunt wordt gebruikt. Toch dient het MKG-bestand niet in de eerste plaats epidemiologische doelen. Dit bestand vertoont volgende tekortkomingen:

- Chronische aandoeningen die meerdere ziekenhuisopnames vergen, zullen worden overgedaan, aangezien herhaalde opnames slechts gedeeltelijk kunnen worden gedetecteerd. De reden daarvoor is dat er pas sinds 2004 unieke patiënt-identifiers beschikbaar zijn. Het aantal herhaalde ziekenhuisopnames varieert afhankelijk van de aandoeningen van minder dan 5 % tot 50 %.
- Het MKG-bestand maakt een onderscheid tussen hoofddiagnose en secundaire diagnose. Welke diagnose moet worden gebruikt, is echter niet zeker; de aandoening lijkt bepalend voor de uiteindelijke keuze. Dit hangt ook af van de regels die voor het coderen van de MKG werden gehanteerd.
- De MKG bevatten enkel informatie over gehospitaliseerde patiënten; minder ernstige gevallen die geen ziekenhuisopname vergen, blijven dus buiten beschouwing.
- Het optimaliseren van de case mix voor financieringsdoeleinden kan leiden tot een overwaardering van bepaalde aandoeningen. De omvang van dit verschijnsel en de mate waarin dit de codering van de hoofddiagnose beïnvloedt, is echter niet gekend.



- De sensitiviteit en specificiteit van de MKG-codering zijn evenmin gekend, maar de evaluatie van deze parameters valt buiten het bereik van dit project. Hoe betrouwbaar de achtergrondincidentie berekend volgens de MKG is, is niet geweten, maar we vermoeden dat die voor specifieke aandoeningen die een ziekenhuisopname vergen groot is. Enkel capture-recapture studies laten toe de betrouwbaarheid te evalueren.

4 UITDAGINGEN EN OPPORTUNITEITEN IN VERBAND MET DE BEWAKING VAN VACCINVEILIGHEID

4.1 Bewaking van de vaccinveiligheid in België

De geneesmiddelenbewaking in België valt onder de wettelijke verantwoordelijkheid van het divisie geneesmiddelenbewaking van het FAGG, een agentschap dat ressorteert onder de FOD Volksgezondheid. Mocht de benadering via de achtergrondincidentie worden geïmplementeerd, dan zou de bevoegdheid voor het bepalen van het geobserveerde aantal PVOV bij het FAGG liggen.

4.1.1 Gegevensvergaring

Het FAGG ontvangt individuele meldingen van beoefenaars van de gezondheidszorg (artsen, apothekers, tandartsen, verpleegkundigen, vroedvrouwen) en meldingen van individuele cases van houders van vergunningen voor het in de handel brengen (HVH), m.a.w. farmaceutische bedrijven. De HVH die door beoefenaars van de gezondheidszorg, of door onderzoekers van klinische proeven, of nog, via wetenschappelijke publicaties op de hoogte worden gebracht van ernstige bijwerkingen, moeten die binnen de 7 of 15 dagen (naargelang de situatie) vanaf ontvangst van de informatie melden aan het FAGG. Ook promotoren van klinische proeven moeten alle Vermoedens van Onverwachte Ernstige Bijwerkingen (SUSAR - Suspected Unexpected Serious Adverse Reaction) die tijdens hun klinische proef optrad, melden en dit zowel voor geneesmiddelen met een vergunning voor het in de handel brengen als die zonder die vergunning. Niet ernstige bijwerkingen in de EU moeten binnen de 90 dagen worden gerapporteerd. Sinds kort worden nog andere bronnen van individuele meldingen aangeboord:

- ook individuen kunnen PVOV rechtstreeks aan het FAGG melden.
- Ook via Vaccinet, een online systeem voor het bestellen van alle vaccins in Vlaanderen dat sinds 2004 operationeel is, kunnen intussen gegevens over vermoedelijke bijwerkingen worden ingevoerd; in hoeverre die optie tegenwoordig al wordt gebruikt, is nog niet geweten.

Afgezien van de individuele meldingen ontvangt het FAGG van de vergunninghouders ook op regelmatige tijdstippen de verplichte Periodieke Rapportage van Veiligheidsinformatie (PSURs - Periodic Safety Update Reports). Daarin geven de vergunninghouders inzage in en een evaluatie van alle ernstige en niet-ernstige bijwerkingen die zich binnen en buiten de Europese Unie hebben voorgedaan. Na 5 jaar moeten ze een globaal overzicht overmaken; dat kadert binnen het dossier waarmee ze de vernieuwing moeten aanvragen van hun vergunning om de producten te mogen commercialiseren. Om de veiligheid te kunnen beoordelen van de geneesmiddelen die bij klinische proeven worden gebruikt, moet de promotor jaarlijks een veiligheidsrapport opstellen van de ernstige bijwerkingen die zich tijdens het klinisch onderzoek hebben voorgedaan en dat overmaken aan het FAGG (Jaarlijkse Veiligheidsrapport, JVR).

Het FAGG evalueert de individuele en gecompileerde meldingen; dit gebeurt onder de verantwoordelijkheid van twee specifieke werkgroepen. Het FAGG wordt in die taak bijgestaan door een team van interne en externe deskundigen. Het FAGG evalueert voor iedere individuele melding de graad van causaliteit en gebruikt daarvoor de causaliteitscategorieën van de WGO (vaststaand, waarschijnlijk, mogelijk, onwaarschijnlijk, niet geklassificeerd of geen classificatie mogelijk). Indien nodig kan de persoon die de evaluatie uitvoert zich voor bijkomende inlichtingen of toelichtingen in verbinding stellen met de melder. Die causaliteit werd in de meldingen van de vergunninghouders of van andere testonderzoekers doorgaans al bepaald.

We onderzochten de vaccingegevens die het FAGG sinds 2008 vergaarde. Tabel 2 toont het aantal vermoedens van PVOV dat jaarlijks aan het FAGG werd gemeld (de gegevens voor het jaar 2012 dekken enkel de eerste helft van het jaar). Jaarlijks worden zowat 200 meldingen overgemaakt. De piek die in 2009 werd vastgesteld, is hoofdzakelijk het gevolg van de rapportering van bijwerkingen van het vaccin Pandemrix dat tijdens de influenza-epidemie werd gebruikt.

Tabel 2 – Aantal vermoedens van postvaccinale bijwerkingen die tussen 2008 en medio 2012 aan het FAGG werden gemeld

Jaar	Aantal
2008	216
2009	352
2010	170
2011	208
2012	85
Totaal	1031

De database bevatte een beperkt aantal dubbels. De meeste meldingen betroffen het HPV-vaccin (Gardasil; 214), het vaccin tegen difterie, kinkhoest, tetanus (Infanrix; 132) en het vaccin tegen de pandemische griep van 2009 (Pandemrix; 93). Een aanzienlijk aantal meldingen betrof meer dan één vaccin en ook andere geneesmiddelen; daardoor is het niet altijd duidelijk aan welk vaccin de mogelijke bijwerkingen kunnen worden toegeschreven (gesteld dat ze een gevolg zijn van het vaccin).

Voor de beschrijving van de ongewenste verschijnselen gebruikten we MedDRA (Medical Dictionary for Regulatory Activities), een medische terminologie voor de classificatie van informatie over ongewenste verschijnselen in verband met het gebruik van biofarmaceutische producten en andere medische producten. Dit woordenboek bevat een mix van diagnoses en symptomen. Hoe de diagnoses werden bepaald, is niet geweten, maar niets wijst erop dat specifieke definities (vb. de classificatie van Brighton) van de PVOV werden gebruikt. Of en hoe de diagnoses werden geverifieerd weet men evenmin, maar vaststaat dat een deel van de ongewenste verschijnselen die aan het FAGG werden gemeld, geen duidelijk verband met vaccins vertoonden, zoals longmetastase, bloederige diarree of secundaire syfilis. Sommige meldingen betroffen het ontbreken van vaccins, problemen i.v.m. de bewaring en het ongepaste gebruik ervan. De exploitatie van deze gegevens is moeilijk en zou zelfs de toepassing van dataminingtechniek vergen. Zelfs bij het correct opnieuw coderen, een aangepaste verificatie van de diagnoses en een



gepaste dataminingtechniek zou de statistische kracht van een willekeurige analyse waarschijnlijk erg beperkt zijn, omwille van het beperkte aantal meldingen. Het beperkte aantal meldingen (merk op dat dit voor alle vaccins samen geldt) wijst erop dat er sprake is van verregaande onderrapportering; de mate daarvan kon echter niet worden becijferd.

In 2008 lanceerde het BCGH het project "Actieve Geneesmiddelenbewaking" met als doel de beoefenaars van de gezondheidszorg ertoe aan te zetten frequenter ongewenste bijwerkingen te melden en de kwaliteit van die meldingen te verbeteren. Het project werd aangekondigd in de Folia Pharmacotherapeutica van januari 2008; daarnaast verscheen op de websites van het FAGG, van het BCFI, van verscheidene professionele verenigingen en van de Medisch-Farmaceutische Comités een oproep tot deelname. Er werden sensibiliseringssessies voor universiteiten, ziekenhuizen en diverse verenigingen van artsen/apothekers georganiseerd. Er werd een online rapporteringstool beschikbaar gesteld; sinds maart 2009 wordt via de Folia Pharmacotherapeutica een meer gebruikersvriendelijke versie op papier verspreid; de melder ontvangt uitvoerigere en een geïndividualiseerde feedback als reactie op iedere melding; en tot slot is er een elektronische nieuwsbrief "VIG-news" beschikbaar op de website van het FAGG die recente mededelingen in het kader van de geneesmiddelenbewaking afkomstig van verschillende bronnen bevat. Ondanks deze inspanningen kon er geen toename van het aantal meldingen worden vastgesteld.

4.1.2 Gegevensanalyse

Het FAGG voert momenteel geen gegevensanalyse uit. De verschillende meldingen worden elektronisch overgemaakt aan en vergaard in de EudraVigilance databank. Deze centrale bewaarplaats bij het EMA (het Europees Geneesmiddelenbureau) bevat meldingen van vermoedens van ongewenste bijwerkingen gerelateerd aan geneesmiddelen die in de Europese Economische Ruimte zijn toegestaan en van geneesmiddelen die centraal staan binnen klinische onderzoeken. De vergunningshouders en sponsors van klinische onderzoeken maken hun eigen meldingen aan de Europese databank over.^b

Het FAGG heeft rechtstreeks toegang tot alle gegevenselementen in EudraVigilance.

Het Europees Geneesmiddelenbureau staat in voor de statistische analyse. Het EMA onderwerpt de Eudravigilance database maandelijks aan de techniek van data mining (PRR: Proportional Reporting Ratio) en maakt de resultaten daarvan over aan de nationale agentschappen van geneesmiddelenbewaking. Het FAGG staat in voor de verdere analyse van potentiële veiligheidssignalen van 20 producten die het EMA formuleerde. Dit gebeurt grotendeels door afzonderlijke controle van de individuele meldingen, waarbij eveneens de plausibiliteit van de associatie tussen het vaccin en de potentiële PVOV wordt nagegaan.

4.2 tekortkomingen en mogelijke oplossingen

Achtergrondincidentie dient om ramingen te maken over het verwachte aantal voorvallen binnen de gevaccineerde populatie en om de potentiële veiligheidssignalen te interpreteren; daarbij wordt nagegaan of het eigenlijke aantal geobserveerde verschijnselen het verwachte aantal al dan niet overtreft. Ook het tellen van de PVOV's en het analyseren van de O/E-ratio's houden een aantal moeilijkheden in. Tabel 3 vat de uitdagingen en opportuniteiten binnen iedere stap van een systeem van bewaking van vaccinveiligheid samen uitgaande van het gebruik van de achtergrondincidentie.

^b http://www.fagg-afmps.be/nl/MENSELIJK_gebruik/geneesmiddelen/geneesmiddelenbewaking/info_icrs - mah_sponsors/

**Tabel 3 – Uitdagingen en opportuniteiten binnen het systeem van bewaking van de vaccinveiligheid uitgaande van de achtergrondincidentie (AI)**

Type	Uitdagingen	Bron	Algemeen	Mogelijke verbeteringen	Specifiek voor België
1. Berekening van de achtergrondincidentie van diagnosemeldingen door ziekenhuizen					
1.1. Onderrapportering	De registratie gebeurde enkel op basis van gegevens van gehospitaliseerde patiënten terwijl een deel van de voorvalen verwerkt werd als ambulante patiënten		<ul style="list-style-type: none"> Focussen op de bewaking van ernstige bijwerkingen van geneesmiddelen die leiden tot een ziekenhuisopname of zelfs de dood tot gevolg kunnen hebben Samenvoegen van de databronnen van 1^{ste} en 2^{de} lijn gezondheidszorgdiensten teneinde te komen tot een globale beoordeling van de voorvalen 	Zie ook paragraaf 3	
	Suboptimale detectie van E door een gebrek aan een standaarddefinitie en/of diagnoseprocedures		Standaardiseren van de casedefinities en - procedures	Het ontwikkelingsplan van CARENET stelt een uitbreiding met de 1 ^{ste} lijn voor, maar de haalbaarheid en timing worden niet gemeld. Er is momenteel geen omvangrijk statistisch materiaal beschikbaar voor de 1 ^{ste} lijn.	
1.2. Overrapportering	Fout coderen (Diagnostic Related Group DRG creep)		Administratieve controles/incentives		
	Ontbreken van een standaarddefinitie en/of van diagnoseprocedures		Standaardiseren van de casedefinities en - procedures		
1.3. Systematische blootstellingsfout	Achtergrondincidentie gemeten in een gedeeltelijk blootgestelde populatie (Observed /Expected, O/E, neigt naar 1)		<ul style="list-style-type: none"> Bewaking toespitsen op nieuwe vaccins Meten van de achtergrondincidentie bij niet-blootgestelde populatie Neem de systematische fouten in de analyse in aanmerking 		
1.4. Tijdloosheid	Wanneer de gegevens vertraagd toegankelijk zijn, is de periode van de AI verschillend van die van de O (Observed), wat problemen oplevert als de AI door de jaren heen varieert		<p>De gegevens moeten sneller toegankelijk worden gemaakt</p> <p>De bewaking moet worden toegespitst op aandoeningen met een AI die door de tijd heen stabiel is (vb. Guillain Barré syndroom)</p>	Minimale Klinische Gegevens MKG-bestand in theorie na 6 maanden beschikbaar. De vertraging neemt geleidelijk af (maar bedraagt in 2012 toch nog 2 jaar). CARENET werkt sneller	Zie ook paragraaf 3

2. Het tellen van O volgens passieve bewaking

2.1. Onderrapportering	Suboptimale rapportering	Verstrekkers van gezondheidszorg "stimuleren" om gevallen te melden Stel ook de consumenten in staat om ongewenste bijwerkingen rechtstreeks aan de bevoegde autoriteiten te melden	Het project "Actieve Geneesmiddelenbewaking" is geen groot succes Dit wordt binnenkort mogelijk
2.2. Overrapportering	Systematische notoriëteitsfout, m.a.w. personen die een bepaald vaccin kregen, melden vaker ongewenste verschijnselen wanneer er in de media meer aandacht aan wordt geschonken	Behoedzame communicatie van de risico's?	
2.3. Differentiële verificatie	<ul style="list-style-type: none"> • Definitie van verschijnsel verschillend voor O en AI • De O is in het kader van bewaking moeilijker te verifiëren dan de AI 	Hanteer dezelfde casedefinities en diagnoseprocedures voor zowel O als E (definities van Brighton)	

3. Tellen van blootgestelde subjecten

	De toediening van vaccins wordt niet voor alle vaccins geregistreerd (afhankelijk van de blootstelling die uitgaat van een overwaardering van de vaccinverkoop)	Gedetailleerd vaccinregister
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4. Gegevensanalyse

4.1. Verwarrend	De gemelde gevallen (O) kunnen individuen betreffen met specifieke kenmerken die zowel verband houden met de PVOV (Post Vaccinaal Ongewenst Verschijnsel) en met de vaccinatie.	Standaardisering volgens leeftijd en geslacht. Ook volgens andere parameters, indien mogelijk	
4.2. Klein aantal voorvallen*	<ul style="list-style-type: none"> • De blootgestelde populaties zijn klein • Zwakke associatie tussen vaccin en PVOV 	Ontwikkelen van een transnationale bewaking (vb. Eudrasurveillance), met een op dat niveau berekende achtergrondincidentie	Het Federaal Agentschap Geneesmiddelen en Gezondheidsproducten maakt al gegevens aan Eudravigilance over**
4.3. Herhaald (meervoudig) testen	De bewaking van de veiligheid is een continu proces	Er dienen duidelijke statistische richtlijnen te worden ontwikkeld, om dit aspect in aanmerking te nemen	

* Dit zal resulteren in een lagere statistische kracht en in de volatiliteit van de O/E-ratio, met het risico op onlogische resultaten

** De gegevens worden gebruikt voor data mining, en niet voor de analyse van de O/E-verhouding

5 VOORUITGANG?

We hebben aangetoond dat de achtergrondincidentie van een aantal ziektes in België kan worden berekend. Hoewel de betrouwbaarheid van die achtergrondincidentie niet met zekerheid kan worden bevestigd, wordt vermoed dat die behoorlijk hoog is voor de incidentie uitgaande van de hoofddiagnose of voor duidelijk gedefinieerde aandoeningen die een systematische ziekenhuisopname vergen, of voor de doodsoorzaken die op de overlijdensakten staan vermeld. Het actuele Belgische systeem voor datavergaring is te sterk gefragmenteerd om een betrouwbare achtergrondincidentie te bepalen voor andere ziektes.

Zoals Tabel 3 aantoon is België niet in staat om alle uitdagingen voor een doelmatig gebruik van de achtergrondincidentie het hoofd te bieden, ook al kan er een redelijk betrouwbare achtergrondincidentie worden geproduceerd. Het onderrapporteren van ongewenste verschijnselen aan de bevoegde overheid en de relatief kleine populatie van vaccinrecipiënten in België vormen twee belangrijke uitdagingen. De laatste uitdaging kan niet worden opgelost en wijst op de nood aan een systeem van veiligheidsbewaking op Europees niveau. Die bewaking op Europees niveau ontwikkelt zich snel.

Als we deze elementen in aanmerking nemen lijkt het niet gepast om te investeren in de ontwikkeling van een benadering volgens de achtergrondincidentie voor de bewaking van vaccinveiligheid in België. Dat betekent echter niet dat de bewaking van de vaccinveiligheid op een dood spoor zit. Het is van cruciaal belang dat de meldingen van PVOV aan het AFMPS worden verbeterd. De rechtstreekse melding van PVOV door consumenten, wat binnenkort wordt geïmplementeerd, zou een belangrijke stap in die richting kunnen betekenen. Anderzijds moet ook worden gestreefd naar een beter meldgedrag bij de verstrekkers van gezondheidszorgen en naar een meer gestandaardiseerde classificatie van PVOV. Om op gepaste wijze te kunnen communiceren over risico's en de risico's maximaal te beperken is er ook een snellere analyse en interpretatie van mogelijke veiligheidssignalen geformuleerd door EMA of andere bronnen noodzakelijk.

De mogelijkheid om alternatieve strategieën van bewaking van vaccinveiligheid in België te implementeren, viel buiten de reikwijdte van dit project. Dergelijke strategieën moeten uitgaan van een algemene beoordeling van de nood aan informatie in het kader van gezondheidszorg in België en moeten uitpakken met een globaal plan voor datavergaring en gegevensanalyse. Merk op dat EMA de techniek van data mining reeds toepast op EudraVigilance, een bestand dat veiligheidsmeldingen aan het FAGG bevat. Ook cohortenstudies en reeksen zelfgecontroleerde cases zouden kunnen worden geïmplementeerd via het IMA-bestand (InterMutualistisch Agentschap) dat zowel gegevens bevat over bepaalde vaccinatietypes als over ziekenhuisopname, overlijden en het gebruik van specifieke diensten van de gezondheidszorg of geneesmiddelen. De haalbaarheid van dergelijke benadering moet verder worden geëvalueerd.



■ SCIENTIFIC REPORT

1 BACKGROUND OF THE STUDY

Immunization safety surveillance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects following immunization (AEFI). The role of safety surveillance program is to identify signals that, upon further evaluation, may lead to the discovery of previously unidentified or unrecognized or insufficiently understood AEFI that could not have been identified in the pre-approval period.⁵ Such adverse reactions can be due to previously unrecognized pharmacological effects of the vaccine, interactions with other drugs or vaccines, factors related to specific patient populations, individual patient factors (such as pharmacogenomic factors), or other factors such as being too infrequent to be identified in pre-approval studies.

It might be also that disease episodes and vaccination occur coincidentally, i.e. the two events are not causally related. The likelihood of such temporal association increases with the numbers of persons that are vaccinated, as during large vaccination campaigns, and with the prevalence of these diseases in the target population.⁶ Misinterpretation of adverse health outcomes that are only temporally related to vaccination may lead to high public concern about vaccine safety and severely damage the public confidence into vaccination programmes. In several countries, large scale vaccination against human papillomavirus, influenza and meningitis have been interrupted after the reporting of severe events.^{6,7} The link between vaccination and these events were later discarded. Long-lasting damages to the vaccination programme are illustrated for instance by the very low vaccine coverage against hepatitis B in France more than 10 years after the initial reports of cases of multiple sclerosis that occurred after vaccination.

Immunization safety surveillance is thus crucial for public health. On the one hand, it allows keeping an eye on the risk-benefit balance of vaccination, and triggering appropriate decision-making when that balance is considered not anymore favorable. On the other hand, it provides an objective basis for reassuring messages to the population and practitioners when concerns about the harmlessness of the vaccination emerge due to publicized coincidental associations with diseases. Safety surveillance can be passive, active, or both, according to the way data collection is

organized. Passive surveillance relies on the spontaneous reporting of adverse events, whereas active surveillance relies on the prospective collection of vaccination and adverse events. The basic principle of data analysis is however quite similar in both type of surveillances: the number of adverse events observed in the vaccinated group is compared to what would be expected under the null hypothesis of no association. If the rate of adverse events among vaccinated people is significantly higher than expected, a safety signal emerges and further signal evaluation is required to assess causality (see paragraph 2.1.2 for more details on signal management). A safety signal is defined as an information that arises from one or multiple sources (including observations or experiments), which suggests a new, potentially causal association, or a new aspect of a known association between a vaccination and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verifyatory action.⁸

Figuring out the expected number of adverse events following vaccination is thus central in safety surveillance. There are several ways of computing it. First, the expected number of a given adverse event can be derived by extrapolating to the population of vaccine recipients the incidence rate of that condition in the general population. This is the so-called background rates approach, which is the focus of this report and is described in more details in chapter 2.1.1. Data mining is another approach. The term “data mining” refers to the use of computerized algorithms to discover hidden patterns of associations or unexpected occurrences in large databases.⁹ It is a self contained approach in that it does not require access to external data sets nor to background rates, i.e. the expected number of adverse event for one specific vaccine is derived from the total database of adverse events reports.¹⁰ It simply attempts to identify adverse events that are reported more commonly for one vaccine than others.¹¹ A third approach is to determine the expected number from the incidence rate of the condition under scrutiny in a group of non-vaccinated people. Although such surveillance is enhanced by the increasing use of electronic patient records, either medical or administrative (claim data), it is more complex than the two previous strategies because individual vaccination status must be registered and a linkage with personal health data must be possible. An example of such system is the Centre for Disease Control and Prevention (CDC)'s Vaccine Safety Datalink (VSD)

(<http://www.cdc.gov/vaccinesafety/Activities/VSD.html>) which gathers data on vaccination (vaccine type, date of vaccination, concurrent vaccinations), medical outcomes (outpatient visits, inpatient visits, urgent care visits), birth data, and census data in 10 managed care organizations (over 9 million people annually, 3% of the US population).

This report will focus on the relevancy and practicality of the background rate approach for immunization safety surveillance in Belgium. The Belgian Federal Agency for Medicines and Health Products (FAMHP) has submitted this question because it is confronted to reports of adverse events after vaccination which may be serious, and has to assess them in its pharmacovigilance mandate to take appropriate and rapid actions on vaccination programmes and risk communication, by informing the public and the health care workers on the potential safety issues. There is currently no active immunization surveillance in Belgium, and data mining methods are seldom used. Thus, the approach based on background rates is central. However, these background data are mostly not available for Belgium. Pharmacovigilance experts at the FAMHP are usually using baseline data from other countries to predict the number of expected events. However, Black et al. has shown a high variability in background rates of specific diseases across countries and highlighted the need for locally relevant data.¹²

The main research question we address here is thus: what is the feasibility of calculating and using background rates of adverse conditions for assessing safety issues in large-scale vaccination in Belgium?



2 BACKGROUND RATES IN SAFETY SURVEILLANCE: OVERVIEW OF ISSUES

2.1 Using background rates for signal detection

2.1.1 Computation

The principle of using background rates of health events (including death) (BR) for detecting safety signals is quite straightforward. For a given background rate, the expected number of health events in the vaccinated population can be calculated, assuming a similar event rate in both the vaccinated and the general population, i.e. assuming that the occurrence of the health event under scrutiny is not associated with the vaccination considered. That assumption can be tested by comparing the number of health events actually observed (O) in the vaccinated population to the number expected (E) given the background rates, and by assessing if the O/E ratio differs significantly from unity. If the O/E ratio is significantly higher than one, the vaccine may be considered a potential risk factor for the health event, and the health event a potential adverse event following immunization (AEFI), although further epidemiological studies will be needed to confirm if the association is causal or coincidental.

Let's assume the following contingency table at the population level:¹³

Table 1 – Contingency table

Health event	Vaccinated		
	Yes	No	Total
Yes	a	b	a+b
No	c	d	c+d
Total	a+c	b+d	a+b+c+d

The background rate of the health event in the general population (BR) can be computed as:

$$BR = \frac{(a + b)}{(a + b + c + d)}$$

The expected number of the health event (E) in the vaccinated population is:

$$E = BR * \text{number of vaccinees} = BR * (a + c) = \frac{(a + b) * (a + c)}{(a + b + c + d)}$$

Therefore, the observed-to-expected ratio (OE) can be expressed by:

$$OE = \frac{a}{E}$$

OE can also be expressed as:¹⁴

$$OE = \frac{a}{(a + b) * \frac{c}{(c+d)}} = \frac{a}{b * \frac{c}{d}}$$

We can test whether the observed number of events is significantly different from the number expected with the simple continuity corrected^c χ^2 statistic:

$$\chi^2 = \frac{(|O - E| - 0.5)^2}{E}$$

^c The 0.5 correction in the numerator improves the correspondence between the percentiles of the discrete Poisson distribution and the continuous normal one.

The P value is derived from tables of χ^2 with one degree of freedom. This statistic is derived from the usual assumption that, under the null hypothesis, the observed number of adverse events (O) is approximately Poisson distributed with mean and variance both equal to E.¹³ However, when O is small, the normal approximation to the Poisson distribution (too skewed) is not appropriate and it is recommended to use the accurate approximation proposed by Byar (cited by Breslow and Day,¹³ p 69). Exact confidence intervals around OE can also be computed (see appendix 1 for formulae and a table presenting the values of 95% confidence limit factors for various values of O).

A neat example of such approach can be found in a recent paper on safety monitoring of influenza A/H1N1 pandemic vaccines.¹⁵ The authors applied a background rate of 6.6 per 100 000 person-years for anaphylactic reaction. This background rate was collected at the European level through the Vaccine Adverse Event Surveillance & Communication (VAESCO) initiative (see chapter 4 for more details on VAESCO).¹⁶ Given that background rate, the expected numbers of health events in recipients of the vaccine Pandemrix™ was 163. As the number of anaphylactic reactions in that group of vaccine recipients was actually 244, the OE was computed at 1.50 (95% CI: 1.31; 1.70), i.e. an increase of 50% in comparison with the number expected. Other recent examples where AEFI reporting rates were compared with expected background rates is the postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine in the Vaccine Adverse Event Reporting System (VAERS) in the USA,¹⁷ or the assessment of increased Kawasaki disease after RotaTeq vaccine.¹⁸

2.1.2 Signal management: prioritization and evaluation

Once the observed number of AEs is greater than what was expected under the null hypothesis of no association, a safety signal emerges. Signal management includes signal prioritization and evaluation. Signal prioritization is a first critical step as in large datasets large numbers of signals can appear, a proportion of which by chance only, and assessing all of them would have major resource implications.¹⁹ It is thus important to define a priori which signals warrant further follow-up, i.e. to define the criteria of an impact analysis.⁵ Strength of signal, whether the signal is new or not, its clinical importance (i.e. seriousness, reversibility,

consequences), the potential for preventive measures and the potential impact on public health are important parameters to prioritize the evaluation of signals.²⁰ The biological plausibility of the association is also an important criterion. An elevated OE ratio of lung cancer in the month following vaccination is unlikely to constitute a safety signal because biological mechanisms and time lag are implausible. Other criteria that could be taken into account are a high media attention or political focus, a vulnerable population being particularly concerned (e.g. infants, pregnant women), or an occurrence during the first few years post launch (new vaccines). Very few impact analysis approaches have been published. Waller et al. reported on the impact analysis developed for use in the UK Medicines and Healthcare products Regulatory Agency (MHRA).²¹ This automated mathematical tool includes two scores (from 1 to 100): the evidence score which evaluates the strength of the evidence (strength of the association, plausibility, reliability of data) and the public health score which summarises the potential public health implications (number of adverse events, the potential health consequences of the adverse events, reporting rate). Plotting the evidence score versus the public health score identifies four categories of attention with different consequential actions.²¹

Priority signals must be evaluated rapidly to determine whether they represent a risk which may warrant further assessment, communication or other risk minimization actions.⁵ A multidisciplinary team-based approach by a Safety Management Team (SMT) generally provides the most comprehensive clinical and pharmaceutical experience necessary to guarantee the quality of a signal evaluation.⁵ Further investigations will be necessary for signal evaluation. Criteria to consider when reviewing a signal from a case series include positive dose-response or re-challenge/de-challenge, biological plausibility or lack of alternative explanations, consistency between cases in the pattern of symptoms and time-to-onset, diagnosis based on objective data and lack of confounding factors in the reported cases.⁵ The signal should be verified in other safety data sources which can include pharmaceutical databases, pre-clinical animal studies, clinical trials, all relevant literature and regulatory databases, for assessing congruence or inconsistency with the original signal. Further epidemiological studies, such as case-control studies or self-controlled case-series, may be carried out to ascertain the causality of

the association observed between the occurrence of the adverse health event and the vaccination.

Following signal evaluation, a signal is classified an identified risk, a potential risk (implying a closer monitoring and further investigation), or an artifact not warranting further action. In case a risk is identified, it must be weighed against the benefits of the vaccination. Whether the risk-benefit balance is still favorable must be ascertained, and subsequent changes in vaccination policy decided. Risk communication and minimization are beyond the scope of this report.

Table 2 – Case study: intussusception after rotavirus vaccine in USA²²

RRV-TV was licensed in August 1998. The Advisory Committee on Immunization Practices (ACIP) recommendations for its use were published in March 1999. From September 1, 1998, through July 7, 1999, VAEs received 15 reports of intussusception among infants who had received RRV-TV vaccine. CDC reported this finding in July 1999 and recommended that health-care providers postpone use of RRV-TV at least until November 1999, pending results of a national case-control study that was being conducted at that time. The manufacturer, in consultation with the US Food and Drug Administration (FDA), voluntarily ceased further distribution of the vaccine in mid-July 1999. On October 22, after a review of scientific data from multiple sources, ACIP concluded that intussusceptions occurred with substantially increased frequency in the first 1–2 weeks after vaccination with RRV-TV, particularly after the first dose. In 1999, ACIP withdrew its recommendation for vaccination of infants in the United States with RRV-TV.

2.2 Challenges and options in pharmacovigilance based on background rates

2.2.1 Counting events

2.2.1.1 Problem definition

In pharmacovigilance based on background rates, both the expected number of health events (E) in the vaccinated group, derived from background rates of that health event in the general population, and the number of events actually observed (O), need to be ascertained with accuracy. However, a number of factors can affect the accuracy of E , O , or both.

First, non-standard definitions of health conditions may lead to unconfirmed diagnoses,²³ resulting in either inflation or underestimation of E . As an example, it was assessed that the Positive Predictive Value (PPV) of hospital discharge diagnoses (HDDs) as a tracer of the Guillain-Barré syndrome (GBS) in Lombardy was only 54.8% and 76.4% for the whole hospital population and for patients specifically discharged from the neurology ward, respectively.²⁴ Basing the computation of BR on such figures would result in inflated E , and thus in a decreased sensitivity of safety signal detection. The same difficulties can also occur for ascertainment of O . In defining what constitutes an adverse event, consideration must be given to the tradeoff between sensitivity and specificity. Broad definitions may enhance sensitivity but result in false signals, leading to substantial effort in verifying outcomes yielding few confirmed results. Conversely, definitions with a high degree of specificity may minimize false signaling but also reduce the sensitivity of the surveillance system.²⁵ One could argue that this is a minor issue if the same case definition is used for assessing E and O . However, this is not always the case. For example, an international voluntary collaboration, the Brighton Collaboration, has begun since 2000 to standardize case definitions of AEs following immunization (<https://brightoncollaboration.org/public>). But the case definitions proposed by the Brighton Collaboration are not applied in other health databases, so as the nature of health events accounted in O vs. E might differ resulting in a down- or upwards biased OE ratio.

Second, the detection of health events themselves can be sub-optimal. Underestimated BR may occur if the data sources are incomplete, as reported for intussusception background rate based on only inpatient data in the USA.²⁶ Overestimates of BR might also occur if the ascertainment is based on claim data and these are miscoded with the purpose of maximizing revenue (for more on this, see the part 2 on the Belgian databases).¹ Biased counting of health events can also present for O. Passive surveillance relies on voluntary submission of cases either by clinicians, patients, manufacturers, or others. In such system, O events tend naturally to be under-reported. However, they might also be over-reported due to the notoriety bias, i.e. when public concern over AEs in association with a given vaccine is triggered by media the reporting behaviours might be selectively affected.^{27,28} Redundant detection of cases by unconnected sources of information may also be a determinant. Again, this counting bias of O can be in the same or in the opposite direction as the E bias.

Third, time lags between the occurrence of health events and their reporting to surveillance authorities may impact the validity of OE ratios. As regards E, the incidence of some health conditions in the general population may be quite stable over time, as observed for GBS, but for other conditions incidence can evolve quite rapidly over time, e.g. the declining incidence of sudden infant death in Belgium since 2003 (see chapter 5.1 for more details on this aspect). If the delays to ascertain BR are too long and the E not referring to the same time period as the O, the computation of the OE ratio may raise spurious safety signals in case of increasing BR, or becomes insensitive if case of declining BR. Timeliness of data collection and analysis of O is also a crucial element for efficient decision-making, particularly for vaccines given during a short period, such as influenza vaccine. It might be necessary to analyze data in "real time" (i.e. as they become available), e.g. before the full length of the risk windows for AEs following vaccination had elapsed or before all data accrue (e.g. there might be substantial lag in the accrual of AEs diagnosed in the inpatient setting). However, many delays usually cumulates between the occurrence of adverse events and subsequent political decisions: the vaccine recipients need to consult a physician, the consulted physicians need to identify the AE and link it to vaccination, the consulted physicians also need to transmit the suspicion of AEFI to the competent authority in a

reasonable time period, the competent authority must gather, clean and analyse the data in a reasonable delay, the competent authority needs to prioritize safety signals and decide of minimizing and communication plan. Fourth, it might be difficult to determine BR excluding all potentially exposed persons, because the latter are not separately identified.²⁹ So BRs can be computed in a population which already includes exposed individuals. For example, when we assess the BR of Guillain-Barré disease at the population level, we include in the denominator individuals who have received vaccinations and might have suffered of Guillain-Barré in relation with their vaccination. Therefore, the OE ratio will be biased towards unity. This bias could occur even in the safety surveillance of a new vaccine, e.g. a same adjuvant may have been used in both previous vaccines and vaccine currently under scrutiny. The extent of this bias depends on the prevalence of the exposure in the general population and the size of the true rate ratio in exposed compared with unexposed persons.²⁹ Where the effect of contamination by exposed individuals is small and the OE ratio is modest, the bias may be ignored. In case of highly prevalent exposure and/or high OE ratio, the bias might be substantial.

2.2.1.2 Options for improvement

First, standardization of case definitions can facilitate collection and comparison of data from clinical trials, epidemiological studies and surveillance systems, as well as comparison across regions. The Brighton Collaboration case definitions (BCCDs) are typically structured with multiple levels of diagnostic certainty, and include a preamble with justification for decisions made by the Brighton Collaboration working group for the specific case definition, as well as guidelines for use of the case definition (<https://brightoncollaboration.org/public>). Draft case definitions are evaluated and validated by a reference group prior to finalization. Following publication, the case definitions undergo further evaluation and implementation in multiple settings, with regular review and revision as necessary.⁸ Use of BCCDs was found more reliable and valid than individual, nonsystematic clinician review.³⁰ Problems may arise however when comparing reported AEs to background rates as the latter are usually not measured using the Brighton Collaboration definitions. A common definition of health events should be used for both E and O as

much as possible. This harmonization might be difficult to achieve when E and O are extracted from different sources with different objectives, e.g. E from administrative databases and O from pharmaco-surveillance, as this is currently the case in Belgium.

Second, the counting bias must be minimized. A coordinated, rapid, and reliable health information system allowing an exhaustive and timely recording of both O and E (but avoiding duplicates) is needed. For E, the health events must be registered within all the levels of the health system, i.e. the 1st, 2nd and 3rd lines of services to avoid an under-estimated estimate of the incidence. Such an exhaustive registration appears difficult in the current Belgian health system: estimates based on Minimal Clinical Data relate only to in-patient data, and networks of general practitioner (GP) surveillance are small-scale. A coordinated linkage of health information across the levels of the health system is lacking. There is the possibility to extend the Carenet project to all providers, but the feasibility, validity and delay of such project still need to be assessed (see chapter 3.2.2 for a description of Carenet). In the current Belgian context, a pragmatic approach would be to limit the surveillance to serious adverse events, i.e. adverse events resulting in death or hospitalization. In such case, the Minimal Clinical Data could be a reliable source of information for computing BR, provided that adverse events are coded genuinely (no diagnosis creep), with a clear-cut case definition, and reported in a reasonable delay. For O, a recent example of post-marketing surveillance of influenza mass vaccination in 29 provinces of China³¹ showed how the reporting performances can be substantially improved if strong incentives for reporting, including a legal obligation, are implemented and if the information can be rapidly transmitted to the analysis level. In the China example, cases had to be reported to county Centre for Disease Control (CDC) within 24 hours after notification by patients (2 hours for serious adverse events), and further transmitted to the National CDC immediately through an online National Surveillance System.³¹ Use of electronic data transmission now allows such short delays. A complementary approach to decrease the under-reporting and improve timeliness might be to involve vaccine recipients themselves in the reporting of adverse events. In 2007, the Medicines and Healthcare products regulatory Agency (MHRA) in UK implemented a direct electronic reporting scheme (“Yellow Card online”) to

encourage consumers^d and healthcare professionals^e to report suspected adverse reactions. The Netherlands Pharmacovigilance Centre Lareb provides electronic forms for healthcare professionals and patients to report suspected adverse reactions (<http://www.lareb.nl/Meld-bijwerking/Meldformulier.aspx>). In the USA, it was also demonstrated that an internet-based reporting of AEs in the VAERS has allowed a more timely and more complete information.³² This electronic service became available to the public in 2002. In Belgium also, suspected adverse drug reactions can be notified electronically to the competent authority (FAMHP, Federal Agency for Medicine and Health Products), but only by health professionals^f. It is however planned to allow direct declaration of suspected adverse reactions to the FAMHP by consumers from year 2012 onwards (personal communication, Jamila Hamdani, pharmacovigilance assessor, FAMHP).

It might also be informative to assess the extent of the AE under-reporting, i.e. the sensitivity of a passive surveillance system. It can be estimated by capture-recapture analysis.^{g,33} As an example, by linking the US national

d

<http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Reportingsuspectedadversedrugreactions/Patientreporting/index.htm>

e

<http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Reportingsuspectedadversedrugreactions/Healthcareprofessionalreporting/index.htm>

f

http://www.fagmp.be/en/human_use/medicines/medicines/pharmacovigilance/data_collection_evaluation_measures/

g

It relies on four basic assumptions. First, the population should be closed or should not change in composition between the times of capture by the various sources. Second, sufficient information should be available in each source to match subjects from different sources in a unique manner. Third, the sources should be independent, i.e., capture by one source should not affect a subject's likelihood of being captured by another source. Finally, each subject should have an equal likelihood of capture, or certain segments of the population should not be more likely than others to be captured.³³

Vaccine Adverse Event Report System (VAERS) data (<http://vaers.hhs.gov/about/index>) and data from a case-control study, the sensitivity of the VAERS to detect intussusceptions after rotavirus vaccination was estimated at 47%.³³ The over-reporting of AEs by vaccination status (notoriety bias) is a poorly vulnerable problem in passive surveillance. However, it is unlikely that such a reporting bias may influence the incidence of serious conditions objectively assessed by clinicians, e.g. sudden death or Guillain-Barré. This said, it could be argued that reporting bias are not that crucial if they affect in a similar way the numerator of BR and the count of AEs in the post-immunization period, i.e. such bias would cancel out because present in both O and E. Such situation can be found if O and E are ascertained with similar procedures, in similar periods and locations.

Third, for reducing biased estimates, BR should be computed in an unexposed population. This could be achieved by a study cohort of unexposed individuals, or by subtracting AEs experienced by the exposed individuals from the BR measured at the population level. In reality, such information is seldom available.

A pragmatic solution is to account for this bias when analyzing OE ratios. Jones et al. provide true relative risks for a range of OE ratios, by prevalence of exposure in the general population.²⁹ For instance, an OE ratio of 2.50 corresponds to a risk ratio of 4.00 if the prevalence of exposure in the population is 20%. Such computation is of course possible on the assumption that the prevalence of exposure is known. OE ratios are probably biased towards unity in most cases of vaccine-associated AEs. This is an important aspect to account for when interpreting safety signals, i.e. underlying association are often stronger than what the signals appear to be.

2.2.2 Counting exposed ones

2.2.2.1 Problem definition

The number of AEs must necessarily be reported to the population exposed in order to decide whether the observed count is in excess of what could have been expected without vaccination and constitutes a signal. However, the numbers of vaccine recipients is often unknown, the number of doses sold by the manufacturer being the only information available. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine in the VAERS provides a recent example of such approach where the AEFI reporting rates were presented per 100 000 vaccine doses distributed.¹⁷ This strategy of using distribution however might result in underestimates of AE rates as the number of events are reported to an artificially inflated exposed population. A good example of this problem was described recently in Denmark where, in 2009, 1 000 000 doses of Pandemrix had been distributed, but only 443 135 doses administered to a total of 339 507 subjects.³⁴ However, in such analytical scheme, the sensitivity of the detection strategy is likely to be low due to an overestimation of the number of vaccinees. The safety signal might be detectable only if a great proportion of the population is vaccinated (e.g. 98% of the 5-25 year population vaccinated against rubella and measles in 2003 in Iran³⁵) and/or the association between the vaccine under scrutiny and the AE is strong. Estimating accurately E in such conditions is thus difficult,²⁵ hampering a genuine evaluation whether there is significantly more observed adverse events than expected.²³ In Belgium, data on vaccines reimbursed to individuals can be obtained in a short delay through the PHARMANET database for the following vaccines: influenza, hepatitis B, chicken pox (only Varilrix), rotavirus, HPV, Haemophilus influenzae type b.^h Vaccines against hepatitis A and B can also be reimbursed for some specific professional categories through the "Fonds des Maladies Professionnelles", but this data is not readily accessible. Strikingly, vaccines administered to children are usually given for free and cannot be traced, except in the Vaccinet registry in the Flemish region (see chapter **Error! Reference source not found.** for ore details on this registry).

^h Vaccine rabique Merieux HDCV is also reimbursed



Influenza vaccines are also proposed for free in a number of institutions and are not registered neither.

2.2.2.2 Options for improvement

A registry of vaccinations with a satisfactory degree of completeness would allow computing accurately the number of expected AEs in the group of vaccine recipients. Such registry has been developed in Denmark³⁴ and Finland,³⁶ for example. Allowing a merge with other electronic sets of health data through the recording of the unique individual identification (ID) number would be a further asset for analytical studies assessing causality, although this step is not absolutely necessary for a signal detection based on the OE approach. In Belgium, information on vaccine recipients can be extracted from claim dataset for a number of vaccines (see 2.2.2.1). For vaccines which are not reimbursed, useful lessons could be drawn from the example of the Vaccinet, provided that such initiative is extended country-wise and to all age-groups. Such extension is foreseen in a near future (personal communication, Pieter Neels, FAMHP).

The absence of vaccination registry does not necessarily preclude a conservative utilization of the OE ratio, i.e. by applying the background rates of AEs to the theoretical population of vaccinees (e.g. using the assumption that every vaccine distributed has been administered), or even to the total population (before-after ecological study) for estimating E, but the caveats of such approach need to be acknowledged, in particular a low sensitivity of the signal detection.

2.2.3 Confounding

2.2.3.1 Problem definition

In the analysis of observational data, covariates other than those of primary interest may distort the association between vaccine and AEs. These are called confounders. Confounding may be positive (spuriously strengthening the observed association) or negative (spuriously weakening the observed association). Age is usually considered to be the most important confounder but others are possible as well (e.g. the healthy vaccinee effect is actually an example of negative confounding³⁷). For example, an association between a vaccine and abnormal crying might be driven by the fact that both events are common in young children. There

may be no association, or an association in the opposite direction, if different age groups are studied separately.¹⁴

2.2.3.2 Options for improvement

Two options are possible here: standardization or restriction.

The OE ratio can be considered as a Standardized Incidence Ratio (SIR). This is a weighted average of the age-specific rate ratios where the weights $w_j = n_j \lambda_j$ are the expected number of adverse events for the vaccinated cohort in the j^{th} age group (n_j being the number of individuals of the cohort in the age-specific group j and λ_j being the background rate in that age specific group j):

$$\text{SIR} = \frac{\sum_{j=1}^J \frac{o_j}{n_j \lambda_j}}{\sum_{j=1}^J \frac{n_j \lambda_j}{n_j \lambda_j}} = \frac{o}{E}$$

Note that the incidence ratio can be standardized for other potential confounders as well, such as the socio-economic status or the health status.

One advantage of the SIR is that it minimizes the variance of the weighted average, assuming that the true rate ratios are constant over age categories. This means that it tends to be less sensitive to numerical instabilities in one or two of the age-specific rates.¹³ The standard error depends only on fluctuations in the total number rather than in the age-specific numbers of adverse events. Note that this approach assumes that the OE ratio is constant across strata, a condition which will not always hold.¹⁴ It also assumes that the number of AEs in the different age strata are uncorrelated.

In practical terms, SIR can be used only if BR have been documented by age groups and the age distribution of the vaccinated group is known.

Restriction is an alternative approach, i.e. assessing OE ratio only within specific strata of the vaccinated cohort which seem particularly relevant, e.g. pregnant women. Here again, the limiting factor will be the availability of BR for the specific subgroup considered. Moreover, BR by very narrow strata might be necessary to get a meaningful analysis. For example, BR of intussusceptions are known to vary up to 10-fold by week of age during the 6 first months of life.³⁸ Therefore, the OE for intussusception among recipients of rotavirus vaccines should be stratified ideally by week of age.

A third option to control for confounding is of course statistical modeling, where the association between vaccination and AEs is adjusted for the presence of confounders. This requires access to individual clinical files. This is however an approach which is more suited for further investigations of the safety signal, given the fact that in signal detection through OE strategy, individual information on non-exposed individuals is unknown.

2.2.4 Analytical issues

2.2.4.1 Problem definition

First, safety signals have to be strong enough to be distinguished from the background noise. If the population exposed is too small, either because the vaccine coverage is low and/or the vaccine is indicated for a limited population group or the country population is small (such as a large number of EU countries), the statistical power to detect safety signals will be reduced.

Table 3 gives the number of E needed to detect a minimal rate ratio of 1.1, 1.5, 2, 3 and 4 with a power of 80% and a (two sided) alpha error of 5%, based on the formula's for sample calculations provided by Breslow and Day (p 278, formula 7.1).¹³

Table 3 – Number of expected events needed to detect a minimal rate ratio of 1.1, 1.5, 2, 3 and 4 with a power of 80% and a (two sided) alpha error of 5%

Rate ratio	Number of expected events needed
1.1	823.7
1.5	38.8
2	11.4
3	3.7
4	2.0

In countries with relatively small exposed population, the absolute expected number of events will be low for most AEs. For example, with a background rate of GBS in Europe of 2.2 per 100 000 person-years, the expected number of cases of GBS in people vaccinated with the Pandemrix vaccine between 1 November 2009 and 30 April 2010 was 76.¹⁵ Such a number of expected event would not allow to detect a rate ratio smaller than 1.4. Safety signals will thus emerge only for adverse effects that are strongly associated with a vaccine, and provided the vaccine covers a large part of the population. Another problem when dealing with low observed or expected numbers of events is the volatility of the OE ratio, i.e. its sensitivity to random fluctuations, raising the risk of highlighting spurious associations.¹⁴

Second, timely identification of signals for a rapid response to emerging health problems requires repeated testing of accumulating data. This increases the odds of finding spurious associations between vaccines and AEs, i.e. false signals (error α).

For more common conditions, such as thrombocytopenia, there will be more events in the baseline than in less common conditions, however, in most cases this does not solve the problem as the attributable risk, the risk of side effects that can that is due to vaccination is also likely to be lower in this case, so that the system should be able to detect rate ratio's of 1.1 or even lower.



2.2.4.2 Options for improvement

Signal detection and evaluation should be done in population large enough. This can be done geographically by aggregating data from several neighboring countries, such as the European Union Drug Regulating Authorities Pharmacovigilance (EudraVigilance) at the European level (<http://eudravigilance.ema.europa.eu/human/index.asp>). However, management of safety monitoring at the European level still needs further harmonization and validation (see chapter 3).

This can also be done time-wise by extending the surveillance over the years on a cumulating exposed population. This does not fit for seasonal vaccines such as influenza, but could for other vaccines. In this latter case, however, the concept of early detection of adverse events is lost, which might be difficult to justify politically and ethically.

As regards minimizing the risk of spurious associations, statistical shrinkage can be used,¹⁴ as well as more stringent rules for defining statistical significance. Repeated testing of accumulating data requires special analytical approaches, such as the Poisson maximised sequential probability ratio test (maxSPRT).²⁵ It is beyond the scope of this report to detail complex statistical procedures for safety surveillance of vaccines.

2.3 Challenges and opportunities for vaccine safety surveillance based on a background approach

Challenges and opportunities in vaccine safety surveillance base on background rates are summarized in Table 4, together with some measures specific to Belgium which are currently under way. Most challenges could be possibly tackled in Belgium, provided a strong and thoughtful political commitment is demonstrated. However, given the small size of the country, and the even smaller population of vaccine recipients, and given the relatively low incidence of important AEFIs, a safety signal detection based on background rates is likely to remain lowly sensitive in Belgium.

**Table 4 – Challenges and opportunities in vaccine safety surveillance**

Type	Challenges	Options for improvements	
		Generic	Belgium specific
1. Estimating background rates from hospital diagnosis reports			
1.1. Under-reporting	Registration only based on in-patient data whereas part of the events are treated in out-patient	Focus the surveillance on serious adverse drug reactions resulting in hospitalization or death Merge data sources from 1st and 2nd lines of health services for getting a comprehensive appraisal of events	See section 3 Extension to 1st line is proposed in the development plan of CARENET but feasibility and timing are unreported. No large diagnosis dataset currently available for 1st line.
	Sub-optimal detection of E by lack of standard definition and/or diagnosis procedures	Standardize case definitions and procedures	
1.2. Over-reporting	Miscoding practice (DRG creep)	Administrative controls/incentives	
	Lack of standard definition and/or diagnosis procedures	Standardize case definitions and procedures	
1.3. Exposure bias	BR measured in a population partially exposed (OE biased towards 1)	Focus surveillance on new vaccines Measure BR in unexposed population Account for the bias in analysis	
1.4. Timeliness	Delays in access to data result in BR relating to a different period as O, which is a problem if BR varies over years	Accelerate access to data	MCD dataset theoretically available after 6 months. Time lag is decreasing progressively (but still 2 years in 2012). CARENET more rapid
		Focus surveillance on conditions with BR stable over time (e.g. GBS)	See section 3



Type	Source	Challenges		Options for improvements
		Generic	Belgium specific	
2. Counting O by passive surveillance				
2.1. Under-reporting	Sub-optimal reporting	« Stimulate » health providers to report	« Active Pharmacovigilance » project not very successful	
		Allow consumers to report adverse events directly to competent authorities	Will be effective soon	
2.2. Over-reporting	Notoriety bias, i.e. the recipients of a given vaccine report more often adverse events when media raise public awareness	Cautious risk communication?		
2.3. Differential ascertainment	Definition of event different for O & BR Ascertainment of O in surveillance is more thorough than for BR	Use same case definitions and diagnosis procedures for both O and E (Brighton definitions)		
3. Counting exposed ones				
	Vaccine administration is not registered for all vaccines (relying on vaccine sales underestimates OE)	Comprehensive vaccine register	Vaccinet will be country-wise and include all age ranges soon	
4. Data analysis				
4.1. Confounding	Cases reported (O) may concern individuals with specific characteristics linked to both the AEFI and the vaccination	Standardization by age and sex. Also by other parameters, if possible		
4.2. Small numbers of event*	Small populations exposed Weak association between vaccine and AEAEFs	Develop trans-national surveillance (e.g. Eudrasurveillance), implying that BR must also be estimated at that level	BCPH already transmits data to Eudravigilance**	
4.3. Repeated testing	Safety surveillance is a continuous process	Develop clear statistical guidance for taking this aspect into account		

* This will result in low statistical power and volatility of the OE ratio with the risk of finding spurious findings

** The data are used for data mining, not for OE analysis

3 BELGIAN DATABASES FOR COMPUTING BACKGROUND RATES

3.1 Introduction & methods

In this chapter we try to make an inventory of databases that could be used to investigate or generate a signal that could be an indication that there is an increase in adverse effects. We used information from different sources.

Van de Sande et al. made an inventory of the Belgian databases in 2006.³⁹ The Belgian Institute for Public Health did a partial update of this report focusing on information that is needed for international reporting on health in the framework of the European Community Health Indicators Monitoring (ECHIM) project.⁴⁰ The Morbidat database of the Belgian Institute of Public Health was further consulted to look for additional databases that could be useful for our purposes. We contacted experts that could provide information on useful databases. For the identified databases, we assessed the available information on the websites, in publications or in the grey literature on the structure of the database, contacted persons responsible for the databases for additional information. On some databases we found published evidence from validation studies.

If it was clear from the onset that information would not be useful, e.g. monitoring of infectious diseases, we did not assess the database further. For potentially useful databases we sought information on a number of criteria that determine the usefulness:

- Access to data,
- Data providers,
- Case definition (signs, symptoms, inpatient or outpatient, any tests),
- Population covered and denominators (including age groups),
- Representativeness of the source population (compared to the Belgian population),
- Timeliness (lag between disease onset and disease report, and lag between report and data access),

- Sensitivity (or ascertainment) of the data source: proportion of all nationally diagnosed cases that are captured by the system. This takes into account the coverage of the system and the level of under-reporting,
- Variables available (age, sex, specific subgroups),
- Other factors potentially influencing the probability of event capture and rate calculation (ex. financial incentives, specific tests required).

Detailed results are given in appendix 2, here we present a summary and discussion of the main findings.

3.2 Description of the databases

3.2.1 Minimal Clinical Data

Minimal Clinical Data (MCD; Minimaal Klinische Data - Minimaal Ziekenhuis data (MKG-MZG) / Résumé Clinique Minimum – Résumé Hospitalier Minimum (RCM-RHM)) is a dataset where data are processed and stored from Belgian hospitals that register discharge data on each sojourn. This registration is compulsory since 1990. The MCD contains patient data (among which year of birth, gender, residence, and anonymous hospital and patient identifiers) and stay data (amongst others year, month and day of the week but, due to privacy restrictions, not the precise date of admission and discharge; length of stay; transfer to another hospital with specification of the type of hospital). It further includes an unbounded number of ICD-9-CM coded diagnoses. This dataset could potentially serve to compute background rates. However, a number of limitations must be acknowledged. Firstly, it does not register patients unless they come in contact with a hospital, leaving out contact in outpatient settings. It does not distinguish between first and follow up visits. Second, another major potential source of bias is a phenomenon described as “DRG creep”, i.e. the systematically and deliberately overvaluing of the case mix. This is mainly due to the way hospitals are financed in Belgium, with the implementation of the Prospective Payment System (PPS), a system wherein hospitals receive a fixed reimbursement to treat patients with a given diagnosis, independently of the length of stay or the type of care; and the use of Diagnosis Related Groups (DRGs) as a measure of case mix, linking a particular DRG to the length of stay (LOS), and determining in this way the total cost and the amount that a hospital is



reimbursed for the care of a specific patient.¹ That this is an important issue, was illustrated for Belgium by a study of Aelvoet et al.,¹ where amongst others thrombocytopenia, a condition that is a vaccine related adverse effect, was shown to be (mis)used for this purpose and is actually used as a triggering condition in audits meant to detect fraud. Third, the patient age is not available but only the year of birth. This is a major obstacle when estimating background rates in the most vaccinated age group, young children.

3.2.2 Carenet

Carenet is a secure message exchange client server platform that exchanges the information about hospital admissions, extent, end of hospitalization and costs of hospitalizations between hospitals and health insurance companies through an electronic system (Internet platform). Carenet generates databases in the 7 health insurance bodies, one of those collects medical information. The database records contain text fields (alphanumeric) where a diagnosis is entered, this diagnosis is given when a hospital stay is extended beyond 14 days and at discharge. In principle an ‘advising medical doctor’ (“adviserend geneesheer/médecin conseil”) goes through and approves the admission. Health providers have the choice between free text or the use of ICD-9-CM codes, with the restriction that they can give 1 principal diagnosis and up to 4 sub-diagnoses. Some hospitals enter the same ICD-9-CM coded data that they deliver to the MCD database but this is not done in a consistent way and text mining techniques are needed to extract and analyze the data. Therefore, Carenet is likely to suffer at least to a certain degree from the same biases as the MCD database while being more difficult to exploit. It has some advantages, it would be faster and the age of the patient can be obtained in a more detailed way.

3.2.3 GP sentinel practice networks

There are 2 GP sentinel practice networks operational in Belgium.

The IPH, Institute of Public Health, runs a GP network that consists of around 200 GPs. This nationwide network represents approximately 1.8% of all Belgian GPs and is representative of the Belgian population. It has been conducting a voluntary surveillance of various health problems since 1985 and has proved to be a reliable surveillance system for a wide variety of health-related epidemiological data e.g. on diabetes, stroke, cancer, accidents.^{41,42} The population covered is not precisely known, but is estimated by a method advised by European Influenza Surveillance Network (EISN): each GP is assumed to cover a population that is calculated by dividing the Belgian population by the number of active GPs in Belgium, by year and by region. Items that are registered change every year; until now no items were registered that could be useful for this study. However, the list of conditions is revised every year, allowing for new events to be registered, based on a public health need.

The Intego network is the first computerized network of voluntary sentinel general practitioners in Flanders. The network is organized within the department of General Practice of the Katholieke Universiteit Leuven and provides data on incidences and prevalence of all diseases in Flanders, but also on laboratory tests and drug prescriptions from 1994 onward. Since spring 2009 the registration network includes 55 GP practices. These are spread across Flanders and represent 1.05% of all GPs working in Flanders. Incidence rates are available on a website per ICPC2 code per year per age-group. In 2008 there were 90 324 different patients seen in 55 general practices, this is the yearly contact group (YCG). Bartholomeeusen et al.⁴³ proposed a method to use the yearly contact group to estimate the entire practice population (estimated to be approximately twice the size of the yearly contact group).

Both sentinel practice network share the same limitations. The first limitation is the relative small sample size given the fact that we are looking for fairly rare events. An expansion to 500 000 persons would be useful, but probably fraught with difficulties, mainly in finding enough GP that are sufficiently motivated to assure a sufficient quality of the encoding (Bartholomeeusen, personal communication). The second important limitation is that it provides information on GP practices, leaving out intramural care. This problem can be partly addressed if reporting back to the GP by intramural caregivers is systematically recorded, but it is not clear to what degree this would lead to reliable estimations of background rates.

3.2.4 Special Solidarity Fund

The Special Solidarity Fund (SSF) reimburses costs of medical treatments that are not covered by the compulsory health care insurance system (or any other insurance) and that are related to rare indications, rare diseases, innovative treatment techniques, chronically ill children and medical treatment abroad. To be eligible for reimbursement by the SSF, the medical treatment has to be expensive, threatening the vital functions of the patient, have a proven scientific value and effectiveness and be prescribed by a specialized medical doctor. There may be no alternative that is reimbursed by the compulsory health care insurance system and the patient may not have other rights for reimbursement from other private or public insurance systems. The budget of the SSF varies substantially over the years. Expenses are often determined by changes that occur in the reimbursement of medical costs in the compulsory health care insurance system. Although part of the diseases are rare diseases that may be eligible for funding, it will be difficult to obtain valid data, mainly for following reasons: interviews with different stakeholders indicate that the fund is not well known and that this is perceived to be a problem, this is reflected in the fact that applications come from a limited number of centers, decision criteria are rather vague, it is a fund of last resort that you can use if all other channels of reimbursement are exhausted, this uncertainty makes that not everybody will choose to apply. These elements make that it is unclear what fraction of eligible patients would end up in the database. Moreover, this fraction is likely to vary over time.

3.2.5 Increased child allowance for disabled or ill children

Children aged 0 to 21 years with a disability or a chronic disease are eligible for an increased family allowance. The degree of disability is ascertained by a physician employed by the social security. A database is kept with information on each submission, diseases are coded in 17 disease groups, according to a system designed by the service itself. For more information the electronic files could eventually be consulted. The service only concerns children where at least one person in the family is employed. For self employed persons other support measures are taken.

3.2.6 Pedisurv

Pedisurv (Pediatric Diseases Surveillance), created in 2002 by the Scientific Institute of Public health (IPH) is a surveillance network involving Belgian pediatricians and GPs from Brussels. Its objective is mainly to study rare infectious disease in children and to monitor the impact of public health measures such as vaccination in this group. This surveillance system is voluntary (no incentives are provided) but active, with forms (or emails) sent to all participants on a monthly basis and zero reporting is requested. Electronic reporting through a dedicated website is possible. For each reported case, a questionnaire is filled in with information on demographics, clinical and vaccine status.

In 2010, 504 pediatricians (35%) and 354 Brussels GPs (36%) have participated; 65% of participants report electronically. However, the sensitivity of the Pedisurv surveillance (i.e. the proportion of all cases detected by the surveillance system) was evaluated for invasive pneumococcal disease in 2005-06 through a capture-recapture study (using 3 sources): sensitivity amounted to 73% for children <5 years.^{2,3} Indeed, the majority of large pediatric wards in Belgium were reporting cases.



In 2012, Pedisurv is covering the following diseases: measles, rubella, mumps, invasive pneumococcal disease, acute flaccid paralysis, congenital rubella syndrome, haemolytic uremic syndrome and varicella hospitalisations. The list of diseases under surveillance is annually evaluated by a Steering Committee and updated according to public health needs. The addition of any new disease is also taking into account the workload of the reporting clinicians. So far, no AEFI has been included. However, Pedisurv has in theory the potential to monitor rare and severe adverse events; the possibility to include intussusceptions has been recently discussed. In terms of access to data, Pedisurv data can be requested to the IPH but a convention needs to be signed. Annual reports are publicly accessible at <https://www.wiv-isp.be/pedisurv/>.

3.2.7 Cause-specific deaths

For each death in Belgium, a death certificate is filled in by a physician, and the cause(s) of death are recorded. This certificate is collected and further filled in by the communes and sent to the relevant Community, where the diagnosis is transformed into codes and data are compiled. Since 1998, more details on the causes of death may be recorded, following the international rules of the WHO and the ICD-10 codes ("International Classification of Diseases - 10th revision"). The deaths certificates from the Brussels region are coded by the Flemish Community. After validation and analysis at community level, the data on causes of death are sent and compiled at national level, at the Federal Public Service (FPS) of Economy.

For each death, a number of diagnoses are given: initial cause of death (main), immediate, intermediate and associated causes. Data on the causes of death can be requested to each Community and a convention needs to be signed. In June 2012, 2009 or 2010 data on causes of death were available, depending on the Community (delay 1-2 years). Flanders also publishes crude data on its website. National data are also available, e.g. on the website of the FPS Economy (<http://statbel.fgov.be/en/statistics/figures/>) or on the Standardized Procedures for Mortality Analysis (SPMA) website of the IPH (<https://www.wiv-isp.be/epidemio/spma/>), but with a larger delay (around 3 years), 2008 data were the most recent data as of September 2012.

3.2.8 The European Mortality Monitoring Project

Euro-MOMO (monitoring of mortality) is a EU-funded project, initiated in 2008 and coordinated by the Statens Serum Institute, Denmark, which conduct mortality monitoring system of all-cause (crude) mortality in 20 EU countries. The objective is to detect, on a real-time basis, the excess number of deaths related to influenza and other possible public health threats across EU. EuroMOMO weekly reports all cause deaths by age groups and has developed a common European algorithm to estimate all cause weekly expected mortality to enable the estimation of excess mortality.

Although this event (all-cause mortality) is not included in the conditions for background rates estimation, the interest of EuroMOMO resides in the development of the method to estimate the expected number of weekly deaths, for real-time analysis, which is applied in every participating country: the expected mortality is based on Poisson regression allowing for over-dispersion, including a secular trend and cyclical component. It also uses a binomial regression to model the distribution of delays in reporting. Standardised indicators are used for the comparison of observed vs. expected (weekly Z-score & Cumulated Z scores; and correction for skewedness of low counts). The EuroMOMO has officially ended in 2011 but activities were taken over by the ECDC (European Centre for Disease Control and Prevention), under the name of the European Mortality Monitoring Project. More details are available at the EuroMOMO website <http://www.euromomo.eu/> and http://ecdc.europa.eu/en/ESCAIDE/Materials/Presentations%202009/ESCAPE2009_Session_19_Gergonne.pdf. In Belgium, EuroMOMO monitoring is conducted by the IPH, which published a description of the Belgian MOMO system.⁴⁴

3.2.9 Vaccinnet

Vaccinnet was initiated in 2004 in Flanders, with the objective of serving as an online ordering system for all vaccines made available for the vaccination program in Flanders. It was made progressively available for school medicine in September 2005 and in 2006 was expanded to all GPs and paediatricians. This system is linked to a vaccination database, which is made available to all users of Vaccinnet. Vaccinnet users have to register vaccination data in a population-linked database to receive their vaccine supplies. Vaccinees (and vaccinators entering data) can be identified with the national registry number or their names. By October 1st 2010 about 57% of GPs and 50% of Flemish pediatricians made use of Vaccinnet.⁴ Considering that all recent vaccinations of well baby clinics and school medicine are documented in the system, the vaccination database of Vaccinnet accounts for more than 90% of all recently given vaccinations. Vaccinnet also allows for the registration of other vaccinations that are not in the vaccination programme, but there is no particular incentive to register it.

There is a possibility to add information on suspected side effects linked to an individual vaccination (a specific form has been developed for it), but it is unknown to which extent this option is used.⁴ There is also a potential to exchange data with electronic medical files, by downloading Vaccinnet data for integration in the medical files. A linkage with other databases could be possible and could give opportunities for e.g. self controlled case series studies, which falls out of the scope of this report.

Wallonia has announced it will progressively implement registration in Vaccinnet from 2013 onwards.

Further details are available at
<https://www.vaccinnet.be/Vaccinnet/welkom.do>

3.2.10 Disease reporting at regional level

A number of conditions are reported and centralized at regional or community level. However, none of them involve potential AEFI. These regional systems include:

- The Communities coordinate the mandatory notification of infectious diseases. This only involves only infectious diseases, no AEFI are included so far. More details can be found on <http://www.vlaanderen.be/nl/gezin-welzijn-en-gezondheid/gezondheidszorg/preventie/meldingsplicht-infectieziekten> for Flanders, <http://www.sante.cfwb.be/index.php?id=718> for Wallonia and <http://www.observatbru.be/documents/sante/maladies-transmissibles.xml?lang=en> in Brussels.
- Kind & Gezin in the Flemish speaking region and the Office National de l'Enfance (ONE) in the French speaking region collect data on childhood vaccination (see <http://www.kindengezin.be/gezondheid-en-vaccineren/vaccinaties/registratie/> and <http://www.one.be/index.php?id=rapports-one>). These data do not involve AEFI (although ONE also reports on infant deaths) but the websites refer to the Drug Agency pharmacovigilance system for AEFI notification.
- IKAROS stands for GelIntegreerd Kind Activiteiten Regio OndersteuningsSysteem. IKAROS is a database meant to be a support for the functioning of the preventive family support, at the operational, strategic and policy level. Data are collected on all children in Flanders from birth. Files on the children are closed if during 15 months a staff member of the regional teams of Kind en Gezin did not have at least one contact with the concerned family. Registration is continuous.



3.3 Conclusion

We can in general conclude that the current Belgian data collection system is fragmented and that background rates based on those are likely to be unreliable. The degree of bias, overreporting and underreporting is likely to differ per condition, but this is difficult to assess as there are not enough databases that are sufficiently independent to allow cross validation with e.g. capture recapture techniques. However, the main problem is probably the fact that there is no integrated information from the first line (mainly GP but also extramural specialist care, as access to specialists is no conditional upon referral by a GP) and hospital care, making the calculation of incidences difficult. This problem is inherent to the way Belgian healthcare is structured. Signals detection based on excess of cases found in the same database could limit the impact of these biases, if you accept the assumption that the bias would not change over time. Attention in the press for a certain condition and changes in fraud detection efforts could however cause secular trends in over and underreporting. Moreover, procedures to access data in the different databases are often lengthy and variable.

4 BACKGROUND RATES IN EUROPE

4.1 General introduction

Information was taken from the VAESCO website.

VAESCO-project is or was a consortium aiming at the development of vaccine safety monitoring system through linkage of large computerized clinical databases and immunization registries, financed by the European Centre for Disease Control and Prevention (ECDC). The consortium with participants from eight European Union Member States used common software (the Jerboa Vaccine module) to look for possible events in each participating database.

The vaccine safety data linkage system was used amongst others to develop age- and sex-specific background incidence data on rare and more common conditions in larger European populations that possibly could be related to the administration of vaccines. Brighton case definitions for events were used when available. The focus was mainly on events that could possibly be related to mass vaccination campaigns against the 2009 influenza A (H1N1) virus pandemic, and should enable to perform analyses of observed versus expected events. Special software, Jerboa®, was developed to help with the analysis and standardization of the data.

4.2 Methods

The study was conducted using nine population based databases across Europe. The following databases were included:

- Italy: HSD (Health Search Database) & Sicily regional database
- UK: GPRD (General Practice Research Database)
- Denmark: registries
- Norway: registries
- Netherlands: IPCI (Integrated Primary Care Information)
- Sweden: registry data
- Finland: registry data
- Spain: BIFAP (« Base de datos para la investigación farmacoepidemiológica en atención primaria ») project

Incidence rates were obtained by applying a retrospective cohort design. In order to obtain stable rates and to look at trends over time, the study period ran from January 2000 up to January 2009.

4.3 Population

The population comprised all individuals who were registered within the databases during the study period and for whom an adequate start and end of follow-up could be defined. The start of follow-up was the date that the person was first registered in the database or start of data collection, whichever is latest. The end of follow-up was patient death, transferring out of the study population or end of data collection, whichever is earliest. Each center needed to create locally a patient file which comprised the following variables: unique patient ID (linkable across the files), start date (start of follow-up: may also be earlier than 2000 for those registered earlier), end date (end of follow-up), date of birth (if no exact dates are available use midpoints (e.g. 15/07) and sex (M/F).

4.4 Outcomes

The events of specific interest (ESI) have been defined by the European Medicines Agency (EMA) and comprise central neurological, peripheral neurological, autoimmune and other conditions:

- Central neurological disorders include: convulsion, encephalitis (including encephalomyelitis and myelitis), demyelination (i.e. Multiple Sclerosis), Bells palsy, transverse myelitis
- Peripheral neurological disorders include: (optic) neuritis, (systemic) vasculitis, Guillain-Barré syndrome
- Autoimmune disorders include: anaphylaxis, autoimmune hepatitis, oculorespiratory syndrome, thrombocytopenia
- Other disorders: spontaneous abortion and sudden unexplained death

All of the ESI can be assessed in the available databases, except for spontaneous abortion and oculorespiratory syndrome, which were therefore excluded from the analysis. For all events, the start date was defined as the date of diagnosis.

Case definitions are according to the definitions developed by the Brighton Collaboration and literature in case of absence of a Brighton definition. Corresponding disease codes were used to extract information on the outcomes from the databases. Owing to differences in disease coding schemes and the use of free text in most medical record databases, terminologies were mapped according to a common terminology system. Databases in PIV SANE use one of four nomenclature systems to describe the events: the International Classification of Diseases (ICD-9-CM and ICD10); the International Classification of Primary Care (ICPC); and the READ Code (RCD) classification. These different terminologies were mapped using the Unified Medical Language System® (UMLS®) followed by extensive manual checking. The UMLS is a biomedical terminology integration system handling more than 150 terminologies including the four used in the PIV SANE project. Database query harmonization followed an iterative process with six stages:

- Event definition using clinical criteria established by the Brighton Collaboration
- Identification of UMLS concepts corresponding to the event
- Discussion among database owners regarding relevance and applicability of the UMLS concepts identified
- Translation of the concepts into the terminology of each individual database
- Extraction of data
- Creation of input files for Jerboa© and verification of output

Each center created locally an event file which comprised the following variables: unique patient ID (linkable across the files), date event (start of disease), event (acronym for disease). The date of the event was the date of diagnosis. Case identification was entirely based on disease codes. There was almost no case validation in this first phase of the study (exception IPCI). It was planned that in a subsequent phase the positive predictive value of the disease codes would be calculated by conducting chart review on a selected number of cases, but it is unclear if this will happen as financing seems to be lacking.



Jerboa® calculated the incidence of disease while differentiating between chronic diseases and intermittent diseases (i.e. convulsions, anaphylaxis, thrombocytopenia and spontaneous abortion). For chronic diseases Jerboa® censored at the first occurrence of the disease. This means that all subjects with an event prior to the start of follow-up (prevalent) were excluded. The run-in period incorporated by Jerboa® to define incident events was varied between 0 years, 1 year and 3 years. Depending on the latency period of the disease a longer run-in may be chosen. For episodic diseases (i.e. convulsions, anaphylaxis and thrombocytopenia) a run-in of

0 could be chosen. Jerboa® calculated rates of episodic diseases on repeated occurrence of the event, following a fixed episode duration of 4 weeks.

Table 5 shows the preliminary age standardized incidence rates per 100 000 person years for persons of 10 years and older. This age was chosen because some countries did not provide data on persons under 10 years. This table is only given as an example, more detailed rates per year, sex, age group are given on the VAESCO website.

Table 5 – Age standardized incidence rates per 100 000 person years for persons of 10 years and older

Event of Special Interest	Italy	UK	Norway	Denmark	Netherlands	Sweden	Finland	Spain	Italy (Sicily)
Autoimmune hepatitis	2.53	1.11	2.68	1.83	0.52	1.00	3.77	2.07	11.79
Anaphylaxis unspecified causes	3.95	6.85	7.27	6.04	0.58	3.40	11.17	1.68	1.42
Anaphylaxis known causes	12.21	0.87	1.25	3.37	3.35	1.96	2.69	1.44	23.96
Bells palsy	33.14	31.68	10.90	16.56	25.59	5.07	29.10	48.03	7.00
Convulsion	72.81	249.63	179.19	301.74	156.70	110.06	377.62	42.74	107.90
Demyelination	16.39	15.88	51.71	18.45	6.09	6.98	39.79	8.90	15.54
Encephalitis other causes	22.72	4.26	5.07	2.78	0.42	2.27	2.77	1.82	2.29
Encephalitis viral	1.15	1.03		1.96	1.20	1.13	3.90	0.66	1.23
Guillain-Barré Syndrome	2.90	1.49	7.75	2.21	1.49	1.36	2.78	1.52	2.23
Optical neuritis	6.00	4.44	2.77	3.74	1.97	0.56		6.11	4.04
Sudden death	0.00		2.68	9.56		0.54	1.66		0.06
Thrombocytopenia	24.00	19.23	6.80	22.21	57.36	7.13	43.25	53.12	14.89
Transverse myelitis	0.02	0.92	0.26	0.77	0.41	0.22	0.93	0.71	
Vasculitis	39.64	19.28	1.80	20.59	65.78	8.49	17.61	28.13	10.43

Background incidences differ rather wildly between countries, despite the efforts to standardize data collection and case definition. On their website this is attributed to the fact that unvalidated code extractions were used and possibly to differences in health care system, coding habits, type of coding library (READ and ICD-9-CM are the most granular), financial incentives for coding and database type. A major concern in the provided rates expressed by the project is the inclusion of false positives in the numerator, which may have occurred especially where less specific codes were included in the search criteria. This may have led to an overestimation of some of the rates. Plans seem to be ongoing to do further validation, but funding would be lacking (Myriam Sturkenboom and Kari Johansen, personal communications).

Despite these limitations, it is fair to say that the databases and data collection systems are vastly better than what is likely to be achievable in the Belgian context, unless there would be a sudden increase in political will to invest in the collection and analysis of morbidity data and integrate better information from the first line and referral structures.

5 ESTIMATION OF BACKGROUND RATES FOR SELECTED CONDITIONS IN BELGIUM

5.1 Sudden Infant Death

Sudden infant death syndrome is the leading cause of death in infants aged 1-11 months of age in the developed world. Background rates of Sudden Infant Deaths (SID) are crucial in post-licensure assessment of vaccine safety because infant primary immunization schedules temporally coincide with the peak age for the incidence of SID. For instance, the EMA regularly requests vaccine manufacturers to perform literature reviews of SID rate to update the observed vs. expected analyses provided in the Periodic Safety Update Reports (PSURs).

5.1.1 Definitions

The lack of pathognomonic features of SID has left it as a diagnosis of exclusion, and a number of definitions have been proposed and used, resulting in discrepancies in rates between studies.⁴⁵ The following definitions are still used today in recent studies:

- In 1989, an expert panel under the US National Institute of Child Health and Human Development (NICHD) proposed to define SID as “the sudden death of an infant under one year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history”.

Because this definition requires an examination of the death scene and review of medical history – that are not always conducted, other international working groups have proposed other case definitions and classifications for SID in recent years:

- In 2000, the concept of “Sudden Unexpected Death in Infancy” (SUDI) was introduced by the CESDI-SUDI group and defined as “the death of an infant which was not anticipated as a significant possibility 24 hours before the death or where there was a similarly unexpected collapse leading to or precipitating the events which led to the death”.⁴⁶ The approach is that the SUDI deaths are divided after



investigation into those for which a specific cause of death is established (explained SUDI) and those which remain unexplained or SID. SID is thus a subset of SUDI.

- In 2004, an international panel of SID experts was convened to re-examine the definition, and proposed a more specific definition and classifications for SID, which is described by the publication by Krous et al. and referred to as “the San Diego definition”.⁴⁷ SID is defined as “the sudden unexpected death of an infant <1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history”. To take into account the non-autopsied cases of presumed SID, a new classification system was proposed. SID are classified into 4 groups, on the basis of the presence of classical SID features and the amount of information available. These definitions are more specific than those developed by the Brighton collaboration (see below).⁴⁸ Under this definition, autopsy is not compulsory to define SID but SID without autopsy are classified under “unclassified SID”. This definition is widely used today.
- In 2007, the Unexplained Sudden Death Working Group, set up by the Brighton Collaboration to develop a case definition and guidelines for reporting unexplained sudden deaths in the first and second years of life, published case definition by levels of diagnostic certainty.⁴⁸ Because vaccines are also administered in the second year of life, the Brighton Collaboration has extended definitions for “unexplained sudden death in the first and second years of life”. In this classification, SID is restricted to deaths in the first year of life which remain unexplained after autopsy.⁴⁸

The VAESCO project, coordinated by the Brighton Collaboration and previously funded by the ECDC, is using the Krous et al. definition but extended it to children <2 years of age (<http://vaesco.net/vaesco/results/abbreviations/SUD.html>). However, VAESCO does not distinguish SID from SUDI.

These differences in definition need to be taken into account when assessing and comparing SID rates across countries and studies.

5.1.2 Literature review

The studies were selected based on the following inclusion criteria: studies from Canada and Western Europe on sudden infant deaths (US studies were excluded because SID rates are higher than in EU countries such as Belgium), published between 01 Jan 2000 and 01 April 2012; English, French and Spanish language; duration of at least one year. The exclusion criteria included: studies from other countries, other periods, other languages, other age groups, shorter periods; studies limited to a subset of children <1 year, i.e. specific age groups that are not targeted for immunization (e.g. early neonatal deaths), specific risk factors or a subset of sudden deaths (e.g. sudden cardiac deaths); SID rate not calculated; studies providing SID rates over larger periods but that do not provide separate rates for periods after 2000. The search terms are described in appendix.

Data from the VAESCO project were also reviewed.ⁱ

5.1.2.1 Background rates

In general, two major sources of SID rates were found: national death statistics based on causes of death statistics from death certificates; and prospective or retrospective specific studies on infant deaths, for which individual SID cases are usually reviewed. These two methods generate different rates because death certificates are most often filled in before the results of further investigation are known. National death statistics thus include a number of deaths that may be later excluded after reception of investigation results.^{49,50}

An international review of SID summarized worldwide data over 1990-2005.⁵⁰ This review is mostly based on national statistics, no case definition is provided and the proportion of SID with autopsy is not described.⁵⁰ A number of 7 national studies describing SID rates in specific countries have been retrieved.^{49,51-56} In addition, 5 studies assessing case definitions and the validity of SID coding have been retrieved.^{45,52,57-59} Rates of sudden deaths limited to infants could not be retrieved from the VAESCO project. Only the most recent rates by country are presented in Table 6 stratified by method.

ⁱ

<http://vaesco.net/vaesco/results/BGR-2010.html>

**Table 6 – Rates of Sudden Infant Deaths (SID) per 1000 live births**

Study/country/period	Design/participants	Rates SID	Sex ratio	Autopsy rate of SUDI	Comments
From national death statistics (death certificates)					
Germany, 200550	National statistics, 1 week to 1 year	0.43	NA	NA	From www.gbe-bund.de
Ireland, 200550	National Death Register, birth to 1 year	0.38	NA	NA	From www.sidsireland.ie
Netherlands, 200550	National statistics, birth to <1 year	0.10	NA	NA	From www.cbs.nl
Norway, 200550	National statistics, birth to 1 year	0.30	NA	NA	From www.ssb.no
Scotland, 200550	General register report, 1 week to 1 year	0.39	NA	NA	From www.statistics.gov.uk
Sweden, 200550	National Statistics, birth to 1 year	0.23	NA	NA	From www.socialstyrelsen.se
France, 200849	National statistics, birth to 1 year	0.33	1.45	NA	No validation. No change of cause of death after post-mortem investigation.
England and Wales, 200752	National Death Statistics, birth to 1 year	0.28	1.64	NA	Deaths coded ICD-10 R95 (compared with R99 to assess diagnostic transfer).
Canada, 2001-05 (except Ontario) ⁵⁶	Linking of live births and death registration, national statistics	0.35	1.50	NA	Deaths coded ICD-10 R95 (compared to other and unascertained deaths to assess diagnostic transfer).
From specific studies					
Sweden, 2001-0553	National Medical birth register, 1 week to 1 year (reviewed)	0.23–0.28	1.39	NA	Deaths coded ICD-10 R95; R95 deaths with other contributory causes of deaths were reviewed and those with conditions that could explain death were excluded.
France, 2007-0949	Prospective survey, birth to 1 year	0.24	1.86	72%	Using Fleming classification. ⁵⁹ No full validation but questionnaire and centralised by a reference centre.
Denmark, 2000-0654	Retrospective analysis of death certificates and autopsy reports	0.22	1.28	87%	Death certificates reviewed by 2 clinicians to classify SUDI/SID, complemented by National Patient Registry data. San Diego classification for non-autopsied SID.



Table 6 and Figure 1 illustrate that studies based on (crude) national statistics, with no or limited validation of diagnosis, yield higher rates compared to those based on specific studies involving validation of diagnosis. Rates per 1000 live births vary across countries, with a range from 0.10 in the Netherlands to 0.43 in Germany. Besides differences in study method, these variations are likely due to difference in case definitions, coding for cause of death, data collection, pathologist preference in coding deaths, but also in practices for autopsy across countries and how non-autopsied cases are dealt with, as a thorough autopsy is needed to distinguish SID from other SUDI.^{49,50,54,55} Some studies also excluded the age <1 week but this should only have a very small effect on the estimated rates because the number of SID occurring in the first week of life is very small.⁵⁰ Variations in rates are also seen within countries.^{49,50,55} SID classically peaks during the 2nd to the 4th month of age and declines rapidly thereafter.⁴⁷ In a French prospective study of SID over 2007-09, two third of deaths occurred at home.⁴⁹

5.1.2.2 *Role of autopsy*

In a prospective study conducted in France in 2007-09, using prospective data collection, an autopsy was performed in 72% of SUDI deaths.⁴⁹ A cause of death was assigned in 40% of SUDI based on autopsy and/or clinical history and additional investigations, allowing to exclude a high number of suspected SID. Indeed, the SID rate found in the prospective study was 0.24 compared to 0.33 found in death statistics in the same period (Table 6).⁴⁹ Similarly, a Danish retrospective study of SUDI cases found a low rate of SID and explained it by the high 49% rate of explained SUDI after autopsy (autopsy rate of SUDI at 83%).⁵⁴

5.1.2.3 *Case definition and coding*

Most of these studies did not use a specific definition for SID or did not specify which definition was used. However, other studies showed that the case definition and the ICD code used may affect the estimated SID rates. The influence of the case definition has been shown in a Danish retrospective study: it found 10% more SID cases by including infants dying while awake while the San Diego definition includes a criteria that the death must occur during sleep.⁵⁴

Death coding in death certificates is usually based on ICD coding. ICD codes for SID are 798.0 in ICD-9 and R95.0 in ICD10. However ICD-10 coding includes other categories of deaths with imprecise causes, under which a true SID case may be coded.⁴⁹ The “unascertained deaths” are defined as those for which the cause remains unknown after investigation, and are usually coded under “other ill-defined and unspecified causes of mortality” or R99 in ICD-10.⁵⁵ Some studies suggested a diagnostic transfer between SID and unascertained deaths, as the numbers of unascertained deaths have risen considerably in some countries.^{52,55,57} For instance in England & Wales, the rate of unascertained deaths has risen by 10-fold over 1995-2003 while the SID rates declined by 50%.⁵⁵ After a working group recommended to stop using “unascertained deaths” as a final cause of death in 2004, the trend reversed: the SID rate slightly increased between 2006 and 2007 while the rate of unascertained deaths decreased by 50%.⁵² Authors recommend to include both groups (SID and unascertained deaths) in any analysis of SID. In Canada however, SID rates declines while no overall increase was observed in unascertained deaths and the study suggested that changes in diagnosis and reporting practices for infant deaths were unlikely to explain temporal decline in SID rates.⁵⁶

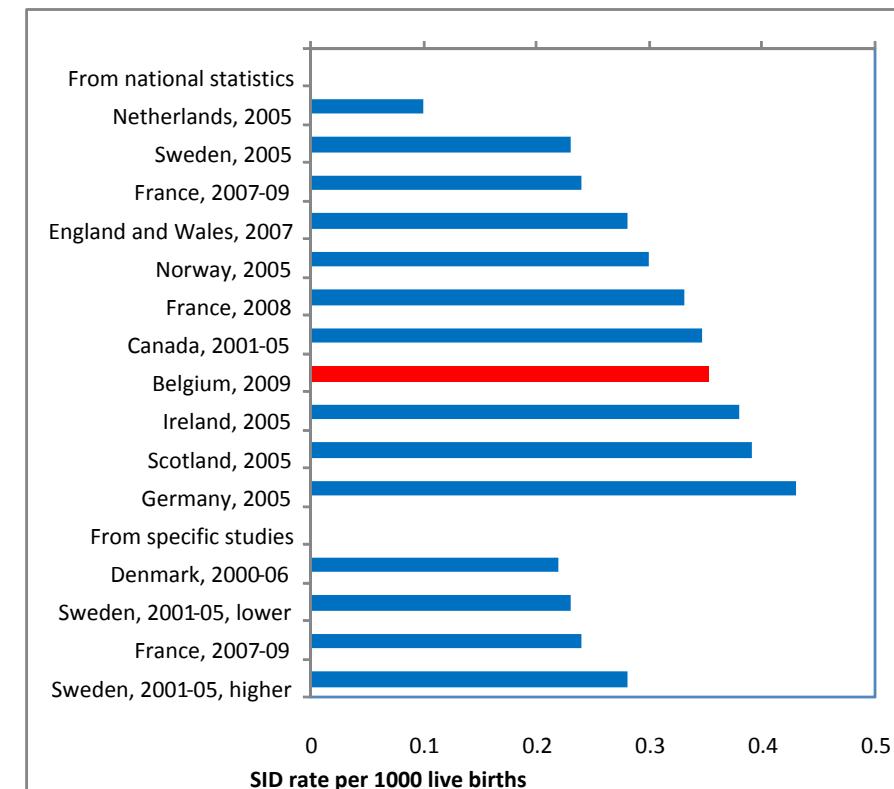
A retrospective analysis of all infant deaths (<1 year of age) in Denmark in 2000-2006 also found that 30% of SIDS were misclassified by the Danish Cause of Death Registry (wrong ICD code or no code).⁵⁴ Another retrospective study in Sweden found a lower degree of misclassification: among the 247 SID deaths coded as R95 in ICD-10 in 1997-2005, the 46 deaths (19%) that had other contributory causes of death were reviewed and 2.4% of SID deaths had other conditions that could explain the death.⁵³

5.1.2.4 Seasonal variations and temporal patterns

SID rates dramatically declined in most countries after the introduction of supine sleeping as the standard position for small infants around 1987-1992 in the EU.⁵⁰ After that, SID rates show different patterns of evolution along time. In some countries such as the Netherlands and Sweden (which show the lowest rates in 2005), SID rates have stabilized after 2000. In the other countries or in Canada, the rates have continued to gradually decline.^{50,56} This decline is likely to be mostly due to declines in post-neonatal mortality rates, following risk-reduction campaign in those countries. However, changes in classification and post-mortem investigations may have also played a role. For instance in England & Wales, the increased use of more thorough post-mortem investigations is thought to have contributed to the SID decline as other causes of death could have been found for a proportion of deaths.⁵⁵ In Canada, the temporal decline in SID rates (-56% between 1991-95 and 2001-05) did not change substantially after adjustment for maternal and infant characteristics.⁵⁶ These recent trends highlight the need to use the most recent rates for any observed vs. expected analysis.

In the French prospective study, seasonal peak were observed in December-January.⁴⁹ In the Swedish study, no seasonality could be statistically detected.⁵³ The same authors showed that seasonality was found during high incidence periods but not during low incidence. It is however unknown whether this is due to low statistical power during low incidence periods or to other factors that were suppressed by changing to supine sleeping position.

Figure 1 – Rates of sudden infant death (SID) per 1000 live births in EU countries and Canada (most recent periods included)





5.1.3 Rates of SID in Belgium

In Belgium, SID data are only available from death certificate statistics, first compiled at regional level and then at national level. According to a study from the Université Libre de Bruxelles in 2001, these deaths corresponded to a larger definition of SID, based on a superficial clinical assessment, and not to the more restrictive scientific definitions of SID. This was due to the lack of standard protocol and of consensus among practitioners, but more specifically to a low recourse to autopsy of suspected SID.⁶⁰ In 2003, a new law stated that an autopsy should be performed in all sudden deaths of infants <18 months, unless one of the parents does not agree, and follow standard protocol in specialized centres.⁶¹ The law also specifies that the death certificate can only mention “sudden death” if the results of an autopsy are presented, but it is unknown to which extent this law has been enforced in our country (see also data on autopsy rates below).

Limited data are published on SID rates in Belgium, and exclusively at regional level. Crude SID data from Flanders are available from Het Vlaams Agentschap Zorg en Gezondheid, which compile death certificates from Flanders.^j A report from the French Community reported a high rate of SID in 1996 (1.08/1000 live births).⁶² A publication from the Brussels region showed a steep decrease in the SID rate in the nineties, with a stabilization at a rate around 0.5/1000 live births in 2004.⁶³

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<http://www.zorg-en-gezondheid.be/Cijfers/Sterftecijfers/Statistiek-van-de-doodsoorzaken/>

Table 7 – Sudden infant deaths (ICD-10 code R95 as initial cause of death) in Belgium, based on death certificates, 2000-2009

Population / year	Mean annual number 2000-09	Mean annual rate per 1000 live births 2000-09	2009 rate per 1000 live births	% SID with autopsy status documented	% with autopsy overall *	% with autopsy 2000-03*	% with autopsy 2003-09*
SID Flanders	26.10	0.41	0.29	88%	60%	53%	67%
SID Brussels	6.50	0.42	0.33	89%	59%	53%	63%
SID Wallonia	23.00	0.59	0.47	87%	59%	57%	61%
SID Belgium	55.60	0.47	0.35	88%	59%	53%	65%
Other ill-defined and unspecified causes of death	1.60	0.01	0.01	45%	80%		

* Autopsy ongoing or planned at the time of death coding

Data sources : Fédération de Wallonie-Bruxelles, Vlaams Agentschap Zorg en Gezondheid and Brussels Region.

Crude data on all deaths coded as Sudden infant death syndrome (ICD-10 R95) in death certificates have been collected from the three regions (Fédération Wallonie-Bruxelles, Vlaams Agentschap Zorg en Gezondheid and the Brussels region), as national death statistics are compiled at national level with a delay of several years. Causes of death were available up to 2009 in Flanders and up to 2010 in Brussels and Wallonia. No case definition for SID is provided and the concept of SUDI is also not defined in Belgium. Over 2000-09, an annual mean of 56 infant deaths were coded as SID as main cause of death in Belgium, corresponding to an annual rate at 0.47/1000 live births in infants <1 year (Table 7). The mean rate is similar across Brussels and Flanders (around 0.4), where deaths are coded by a single team, but higher in Wallonia (0.6). Figure 2 shows an overall decreasing trend over time in SID rates from 0.71 to 0.35 from 2000 to 2009, which is comparable in each region (Figure 3). The age distribution (Figure 4) indicates the classical peak at 2-4 months of age in all regions and a rapid decline in older ages. The week of death was only available for Flanders data; no clear seasonal pattern is observed, except for a lower frequency in the summer break.

Among these deaths, around 60% had an autopsy ongoing or planned at the time of death coding. This proportion is similar across regions but increased slightly over the period, from a mean of 53% until the law was issued (2000-2003) to 65% hereafter (2004-09). Only few infant deaths were coded as “other ill defined and unspecified causes of mortality” (R99, mean <2/year) and this number was stable over the period, suggesting that a diagnostic transfer has not occurred between these entities in Belgium, as described in a few EU countries. The rate of autopsy was slightly higher in this limited group (80%).

In an additional 1.7 infant deaths per year, SID was reported as another cause of death (immediate or associated), while diagnoses such as respiratory disease or congenital disorders were coded as main cause of death. Additionally, 1.1 SID deaths (2%) per year had another diagnosis in other causes of death, including four conditions that could be a cause of death and be revealed after autopsy. Excluding these deaths would only marginally affect the SID background rates.

As illustrated in Figure 1, the recent rate in Belgium is comparable to those reported in other EU countries, and is closest to the rates from Canada, France and Ireland.

Figure 2 – Rates of sudden infant deaths and autopsies in Belgium, 2000-2009

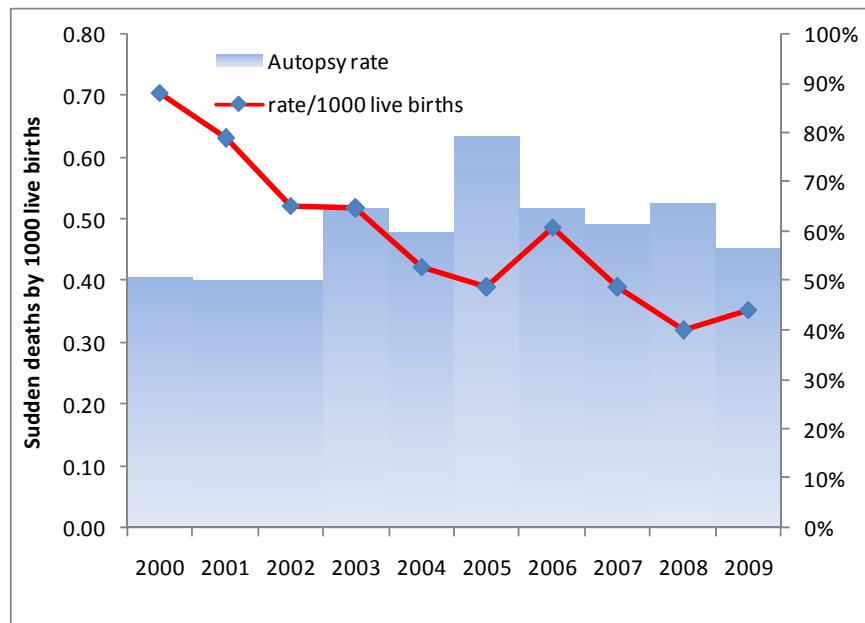


Figure 3 – Sudden infant death rates in Belgium, by region, 2000-2009

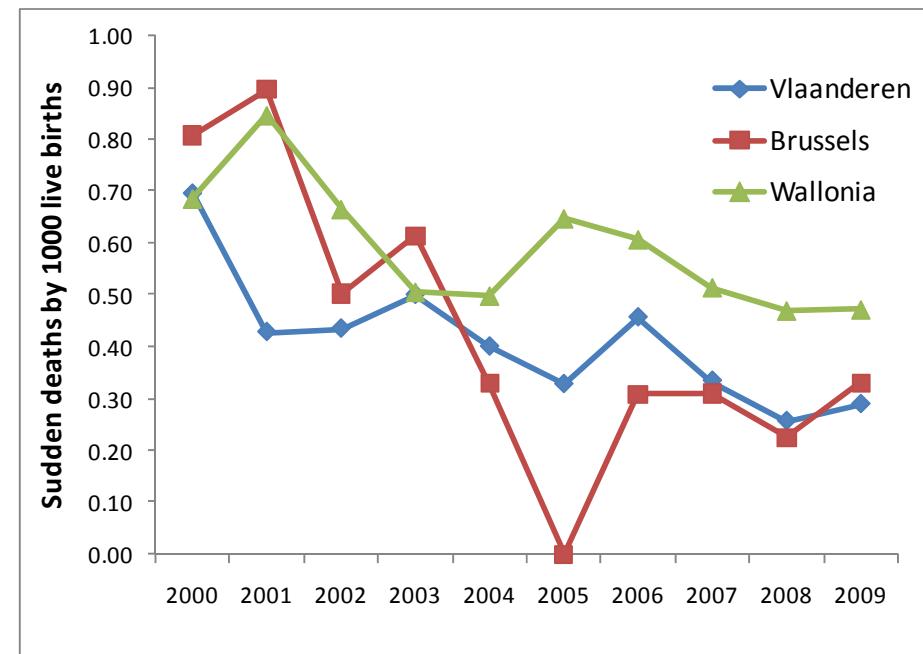
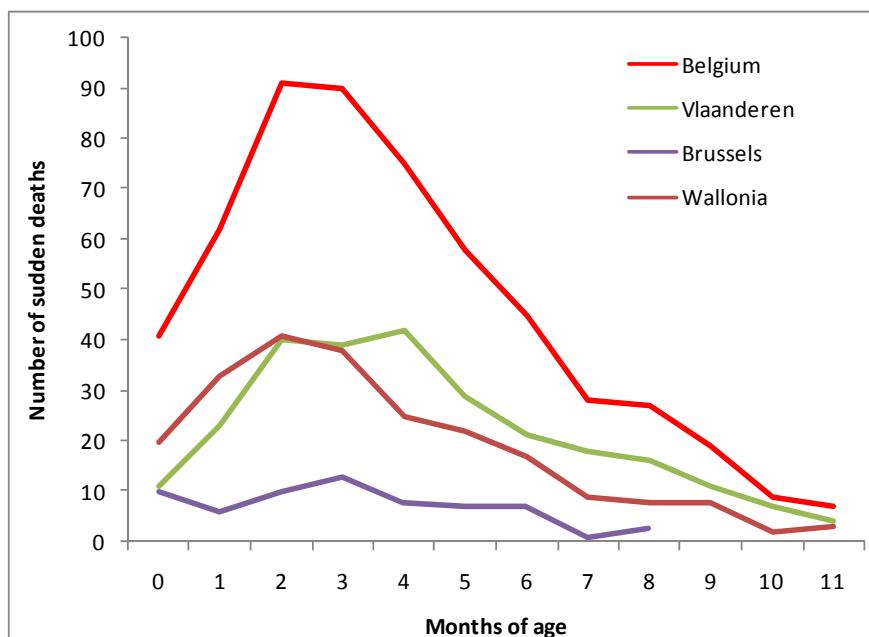


Figure 4 – Number of sudden deaths by month of age, by region, 2000-2009



5.1.4 Conclusions on sudden infant deaths

Rates vary in the literature, due to wide variations in case definition, coding habits, whether diagnoses are validated or not and whether autopsies are systematically conducted. Rates from specific studies, involving diagnosis validation and a higher autopsy rate display lower SID rates due to the exclusion of a proportion of sudden deaths for which a cause has been found after investigations. Rates calculated from Belgian death certificates are similar to those calculated on national death statistics in other EU countries. Regional variations are found (Wallonia rates are higher), which may be partly explained by differences in coding deaths, but the patterns over time and by age are similar. No diagnostic transfer has been identified in Belgium. Rates tend to decrease over the recent years, while the rate of autopsy tends to increase since a new law has been issued, requesting an autopsy to establish a diagnosis of sudden death.

The Belgian data on causes of death seem appropriate to calculate background rates of sudden deaths in Belgium. The most recent rates should be used due to temporal trends and may be available at regional level (1 to 2 year delay).

5.2 Sudden death with unknown cause in ≥ 1 year of age

5.2.1 Rationale

Background rates of sudden deaths in other ages are important in post-licensure vaccine safety assessment when large campaigns target several cohorts, such as the annual influenza vaccine campaign or the HPV catch up vaccination of adolescents.

5.2.2 Definitions

As opposed for sudden infant deaths, there are no standardized definitions for Sudden Death (SD). SD is defined by the World Health Organization (WHO) as natural, unexpected death occurring within 24 hours after the onset of symptoms.⁶⁴ However, the time elapsing between the onset of (final) symptoms and death is controversial and may be as short as 1 hour in a number of sources.⁶⁵⁻⁶⁷ In ICD classification, sudden death with cause unknown corresponds to the codes R96 in ICD-10, which exclude sudden infant deaths whose aetiology differs and cardiac deaths, or to 798.1 and 798.2 in ICD-9 (Table 8).⁶⁴ The code R96, which is mostly used nowadays in cause of death statistics, includes “instantaneous death” (R96.1) and “death occurring less than 24 hours from onset of symptoms, not otherwise explained” (R96.2). Additionally, the diagnosis of “other ill-defined and unspecified causes of mortality” (R99 in ICD-10) may also include sudden deaths with unknown cause. Sudden deaths due to specific causes, such as cardiac or respiratory causes, may be coded under a corresponding ICD classification. A literature review on SD retrieved more than 30 ICD-10 codes that were used in 17 relevant publications on the topic.⁶⁸



Sudden unexplained deaths (SUD) are generally defined as SD in the absence of a diagnosis despite autopsy and, in settings in which autopsy is not mandatory, this concept includes SD in which no autopsies are performed.⁶⁹ It is unclear from the literature to what extent this concept corresponds to the sudden deaths with cause unknown; the definitions are very similar but the concept of SUD generally defines how non-autopsied deaths are dealt with. The concept of sudden *unexpected* death (abbreviated as SUD as well) seems to correspond to the above definition of SD but some criteria are added.⁷⁰ The Brighton Collaboration has only defined unexplained sudden death in the first and second year of life.⁴⁸

Table 8 – Concepts of sudden deaths and definitions (excluding sudden infant deaths)

Concepts	Sources	Definitions
Sudden death (SD)	WHO ICD-10, 2012 (R96.1 and 96.2) ⁶⁴ , Vaartjes, 2009 ⁶⁸ De la Grandmaison, 2006 ⁶⁵ , Eckart, 2004 ⁶⁶	Death occurring less than 24 hours from onset of symptoms, not otherwise explained. This includes death known not to be violent for which no cause can be discovered and death without sign of disease. Natural, unexpected death within 1h of the onset of final symptoms (or inciting event)
Sudden unexplained death	Van der Werf, 2010 ⁶⁷ Tan, 2005 ⁶⁹ Eckart, 2011 ⁷¹	Death in absence of a diagnosis despite autopsy. SD in patients with no relevant medical history in whom post-mortem analysis is not conducted and in the sizeable proportion of patients in whom detailed post-mortem studies fail to provide a diagnosis. Any SD unexplained by pre-existing disease and without identifiable cause on post-mortem examination
Sudden unexpected death	Lim, 2010 ⁷⁰	SD in an apparently healthy subject or in one whose disease was not so severe that such an abrupt outcome could have been predicted
Sudden cardiac death	Eckart, 2011 ⁷¹	SD if autopsy confirmed heart disease with clinical circumstances consistent with a potential cardiac aetiology of death

This literature review and the analysis of Belgian data focused on sudden deaths with cause unknown (R96.0 and R96.1 in ICD-10) and other ill-defined deaths (R99). A methodological obstacle in the validation of the diagnosis of sudden death in studies is that death certificates do not include information on the duration of preceding symptoms.^{68,72}

5.2.3 Literature review

The studies were selected according to the same criteria as described for sudden infant deaths, with the exception of different codes (R96-R99) and age (≥ 1 year); the search terms are presented in appendix. As the search terms, even using additional filters, retrieved more than 4000 publications and mostly non relevant studies, we search for the last literature review on the same topic. The last literature review was published in 2009 and the search for primary studies was limited to the period after the review search date, i.e. 2008 onwards.⁶⁸ Studies that covered only deaths that were autopsied were also not included because they represent a subset of all sudden deaths. Data on sudden deaths from the VAESCO project could not be used because they mix SID and other sudden deaths, provide rates by 5-year age groups only and only limited description of the methodology.^k However, the age distribution of SD was compared to the Belgian age distribution for sudden deaths.

Most studies on sudden deaths focus on cardiac causes of death in young adults because these are responsible for most sudden deaths: in people aged above 35 years, coronary artery disease is the major cause of sudden death while cardiomyopathies are more frequently encountered in those under 35 years.⁶⁵ A high proportion of SD studies are limited to athletes or death after sportive activity. The 2009 literature review on sudden deaths and sudden cardiac deaths included 17 publications but only 3 of them covered periods that included 2000, one was conducted in the included countries but only covered Sudden Cardiac Death (SCD).^{68,73} In the period after the review (2008-2012), very few studies describe sudden deaths or sudden deaths with cause unknown; only two primary studies were retrieved as providing data on sudden deaths from unknown cause (or sudden unexplained deaths) or all sudden deaths or all ill-defined and unknown causes of death.^{68,74} In addition, 13 other studies

described related information on definitions, coding and autopsy rates.^{65,67,69,70,72,75-82} Websites on national death statistics from EU countries also allowed to retrieve some additional data on causes of death.

5.2.3.1 Background rates of sudden deaths in ≥ 1 year of age

Only one Dutch study estimated rates of sudden deaths from unknown causes in subjects aged 1-39 years of age.⁶⁸ This study identified 178 deaths with code R96 in the 1-39 years of age in 1996-2006, corresponding to a rate of 0.19/100 000. These deaths represented only 9% of all sudden deaths. The incidence of all SD was 2.07 per 100 000 in this group and 78% of those were SCD. This study also performed a literature review and found incidence of all SD ranging 3.3-4.6 per 100 000 in older studies in various age groups included in the 1-40 years; incidence of SD from unknown cause (R96) was not computed, but 19% of all SD were attributed to that group.⁶⁸ In Germany, the rate for R96 in 2010 was 0.4/100 000 in all ages while R99 was the cause of death in 14.2/100 000 persons, according to National Death Statistics; the combined rates for ICD codes R96, R98 and R99 in all ages amounted 21.7/100 000.¹ In France (2008), the rate of deaths coded as R96, R98 and R99 accounted for 18.42/100 000 in all ages.⁷⁴

Another older and non-included Spanish study (which covered 1990-1997) estimated an incidence of 1.7 sudden unexpected non-violent deaths per 100 000 persons per year in the 1-19 years, and 32.3% were unexplained after review, resulting in a rate of approximately 0.55 unexplained sudden deaths per 100 000 in this age.

Significant differences in SD incidence across regions were found in two studies from Denmark and the Netherlands.^{72,75}

Only a few proportion of SD occurred in hospitals. The sudden death took place at home in 68% of SCD in 1-39 years of age in Denmark and 22% occurred at work or in a public area.⁷⁶ An US study on SCD found that 82% of cardiac arrests took place at home and 2% in community services.⁸²

^k <http://vaesco.net>

¹ http://www.gbe-bund.de/oowa921-install/servlet/oowa/aw92/WS0100/XWD_PROC?XWD_426/2/XWD_CUB_E.DRILL/XWD_452/D.946/14719

Table 9 – Rates of Sudden Deaths (SD) in persons >1 year of age

Study/country	Design/participants	SD with unknown cause per 100 000 (R96)*	SD with other ill defined cause per 100 000 (R99)	SD (all) per 100 000	Comments
Netherlands, 1996-2006 ⁶⁸	National death statistics in 1-39 years, ICD primary cause	0.19 in 1-39 years*	NA	2.07 in 1-39 years	Based on ICD codes only, no validation of diagnosis
Belgium, 2002-09 (see below)	National death statistics in 1-39 years, ICD primary cause	0.25 in 1-39 years	0.4 in 1-39 years		Based on ICD codes only, no validation of diagnosis
Germany, 2010 ¹	National death statistics in all ages	0.40 in all ages	14.2 in all ages		R99 ranked as 17 th cause of death
Belgium, 2002-09 (see below)	National death statistics in all ages, ICD primary cause	5.7 in ≥1 year	2.0 in ≥1 year		Based on ICD codes only, no validation of diagnosis

* Calculated from the numerator and denominator provided in the publication

5.2.3.2 Role of autopsy

The autopsy rate of sudden deaths in adults is rarely described. In a Danish study on SUD among young aged 1-35 years, the nationwide autopsy rate was 75%,⁷⁶ but was higher in the 1-19 years old compared to the 20-35 years old.⁷⁵ The same study revealed significant regional variations in the autopsy rate of this group, but was not able to adjust the analysis for socioeconomic status. The study concluded that non-autopsied cases might play a significant role in the measures of SD rates. In an US study, an autopsy was conducted in 12% of the sudden deaths identified as SCD of all ages.⁸²

5.2.4 Rates of sudden deaths in Belgium

Crude data on all deaths coded as “ill-defined and unknown causes of mortality” (ICD10 R96 to R99) in death certificates have been collected from the three regions. Data from Wallonia were not available for 2000-01 and Flanders data were not available for 2010; analysis at national level has thus been restricted to the period 2002-09.

Over 2002-09, an annual mean of 594 sudden deaths with cause unknown (R96) were reported as main cause of death in Belgium, corresponding to an annual rate

of 5.7/100 000 (Table 10). This rate varies widely across region, from 2.3 per 100 000 in Wallonia to 12.8 in Brussels (Table 10 and Data sources : Fédération de Wallonie-Bruxelles, Vlaams Agentschap Zorg en Gezondheid and Brussels Region).

Figure 5). These differences do not reduce after standardization for age (using as reference the Belgium population, data not shown). However, coding practices for deaths seem to differ across regions: in Wallonia, where the rate of sudden death (R96) is the lowest, the number of “other ill-defined and unspecified causes” (R99) deaths represents 2.2 times the number of sudden deaths while this code accounts for only 9% of sudden deaths in Flanders and Brussels. If we add the other ill-defined deaths to the sudden deaths with cause unknown, the SD rate amounts to 7.7 and is similar in Wallonia and Flanders (Table 10 and Data sources : Fédération de Wallonie-Bruxelles, Vlaams Agentschap Zorg en Gezondheid and Brussels Region).

Figure 5), especially in the most recent years (in 2009, 6.8 and 6.7/100 000, respectively). It should be noted that the causes of death from Brussels are coded by the team of Flanders. However, coding practices also seem to differ between these two regions: sudden death with cause unknown is coded as an *immediate* cause in a higher proportion of deaths in Flanders (67% of all sudden deaths) compared to Brussels (36%). If we

add the sudden deaths coded as immediate cause to those coded as *main* cause, the differences in rate would reduce between Flanders and Brussels (Table 10), especially in recent years (21.4 and 18.7 per 100 000 in 2009, respectively); immediate causes of death were not requested from Wallonia. Another contributing factor to the higher rates in Brussels may be that the region of death does not correspond to the residence of the deceased but to the place of death (due to delays in receiving death certificates from the other regions and outside Belgium). As Brussels is concentrating major hospitals, we can expect that more inpatient deaths occur in the capital region. The definition of sudden death (≤ 24 hours after onset of symptoms) does however not suggest that most deaths would be hospitalized; in a US study, 82% of SCD occurred at home and this is not expected to differ for SD from unknown cause.⁸² However, it is possible that a part of the Brussels deaths were residents from other regions and deceased when staying in Brussels for professional or other reasons.

Table 10 – Sudden deaths in Belgium, based on initial (main) cause of death, annual means for 2002-2009

Region	Number sudden deaths (R96)	Number ill-defined deaths (R99)	Mean rate of sudden deaths per 100 000 (R96)	Mean rate of ill-defined deaths per 100 000 (R99)	Mean rate of sudden and ill defined deaths per 100 000 (R96+R99)	Mean rate of sudden and ill defined deaths per 100 000 (R96+R99) initial and immediate
Flanders	387	31	6.4	0.5	6.9	20.5
Brussels	129	11	12.8	1.0	13.9	28.8
Wallonia	78	172	2.3	5.1	7.4	NA
Belgium	594	212	5.7	2.0	7.7	NA

Data sources : Fédération de Wallonie-Bruxelles, Vlaams Agentschap Zorg en Gezondheid and Brussels Region.

Figure 5 – Annual rates of sudden deaths (R96 left), other ill-defined causes (R99 middle) and both causes (right), by region, over 2000-2010

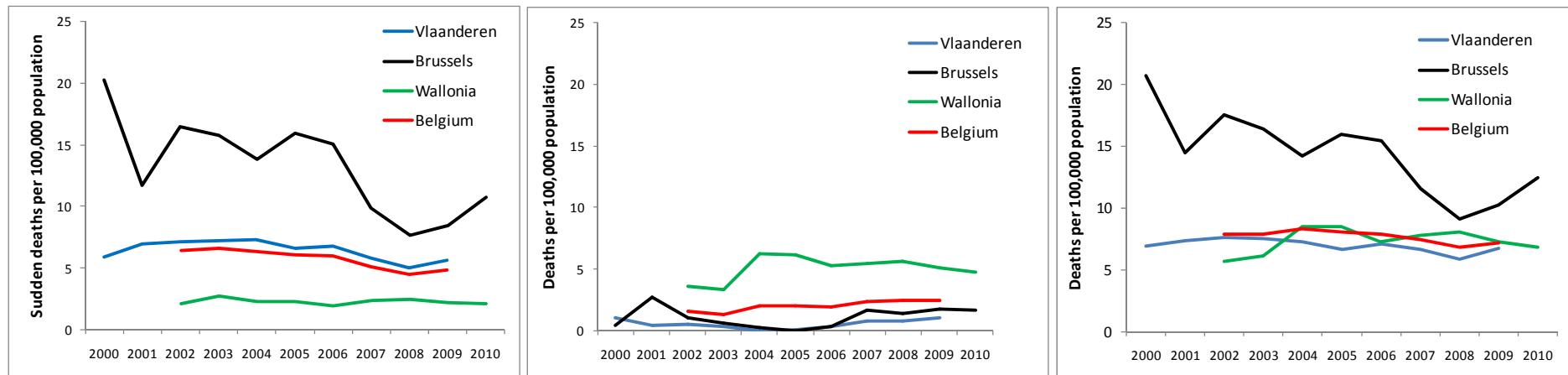


Figure 6 – Annual rate of sudden deaths (R96) by age group, Belgium, average 2002-09

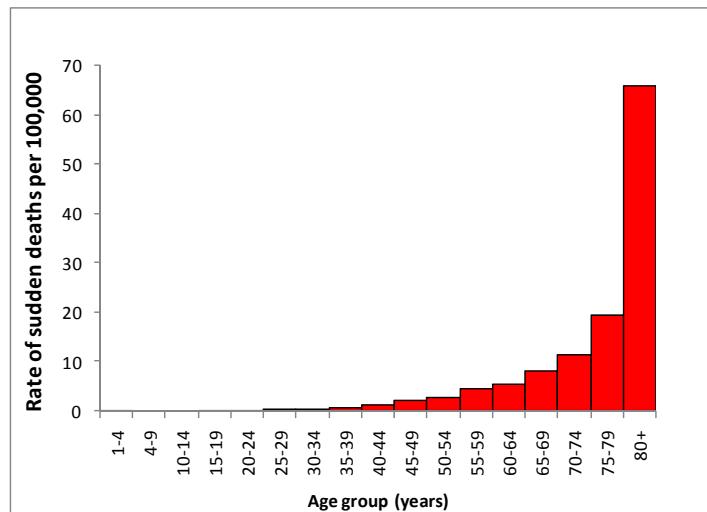
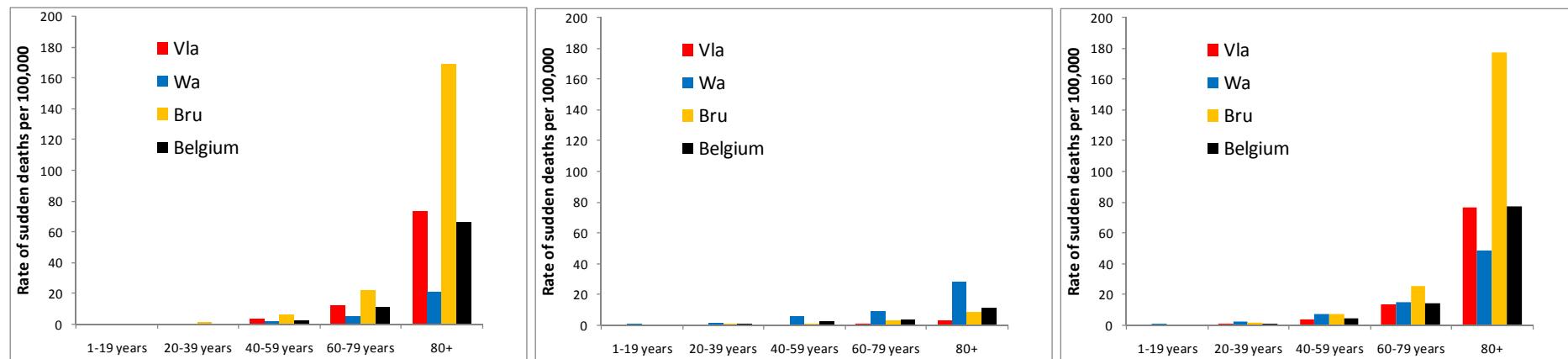


Figure 7 – Mean annual rate of deaths due to sudden deaths (R96 left), other ill-defined causes (R99 middle) and both (right) by age group and region



Data sources : Fédération de Wallonie-Bruxelles, Vlaams Agentschap Zorg en Gezondheid and Brussels Region.

Figure 5 (left) shows no clear trend over time in annual rates of sudden deaths with unknown cause from 2000 to 2009, overall and in each region, although a slight decrease cannot be excluded in Flanders over 2002-08. The rate of other ill-defined deaths (R99, Data sources : Fédération de Wallonie-Bruxelles, Vlaams Agentschap Zorg en Gezondheid and Brussels Region.

Figure 5 middle) does not show an increasing trend over the study period, suggesting that coding practices have been relatively stable across the recent years. The age distribution of sudden deaths with cause unknown (R96) shows that rates gradually increase with age, as could be expected (Figure 6). Age-specific rates of sudden death also vary largely across region and by ICD code (Figure 7), with a particularly high rate in the ≥80 years of Brussels. Similar patterns are seen for other ill defined causes of death (R99).

These rates can be compared to a few other studies. The Belgian rates based on R96 as initial cause of death are close to those estimated in the 1-39 years in Netherlands in 1996-2006 (0.25 vs. 0.19 per 100 000

respectively, Table 9). Conversely, Belgian rates markedly differ from the German rates, with a much higher rate for R96 and a lower rate for R99 as main cause of death (Table 9). The age group differs (<1 year included in Germany) but different practices in coding deaths are likely to contribute. The Belgian rates measured in the 1-19 years are lower than those measured in a Spanish study (0.30 vs. 0.55 per 100 000 respectively) but that study covered an older period (1990-95).

The week of death was only available from Flanders, where the numbers of sudden deaths were 19% higher during autumn-winter (weeks 41-13) compared to spring-summer (week 14-40). Data on autopsy were only available from Flanders and information was available for 94% of sudden deaths: certificates report that an autopsy was under way or planned in only 2% of the sudden deaths (R96). This proportion was substantially higher in the adults <50 years of age (14%) compared to the elderly (1% in the ≥60 years of age and <0% in the ≥80 years). The autopsy rate was also higher (14%) in deaths coded as other ill-defined deaths (R99).



5.2.5 Conclusions on sudden deaths

We found differences in definitions of sudden death, practices in coding deaths and rates of autopsy across countries, as well as within countries. These variations likely play a role in the discrepancies in background rates of SD across countries, and preclude the use of other countries data to estimate background rates. Belgian data on sudden death are available from death certificates and can be requested at regional level. The advantages are the easy access to the data (on request), rapid availability compared to published studies (e.g. most 2010 deaths were available in mid-2012) and comparability of data with safety signals as these rates are directly based on death certificates. The disadvantages are the lack of validation of sudden deaths, low rate of autopsy (compared to a high rate expected from safety signals), discrepancies in coding across regions and the need to compile three different datasets (with different structure).

5.3 Guillain-Barré Syndrome

5.3.1 Rationale

Guillain-Barré syndrome (GBS) is an acute inflammatory demyelinating disease of the peripheral nerves. The underlying aetiology is not completely understood but is thought to be an immune-mediated process, usually triggered by an acute infection.⁸³ Vaccines are another potential factor and associations between vaccines and GBS have been reported, although underlying mechanisms are not yet elucidated.⁸³⁻⁸⁶ GBS is thus an important focus of vaccine safety monitoring and background incidence rates of GBS are important in signal detection.^{87,88}

5.3.2 Definitions

Among the adverse events following immunizations, neurologic events are among the most severe and the most difficult to assess.⁸⁹

In 2009, the Brighton Collaboration GBS working group developed a standardized case definition for GBS and its variants to facilitate international comparison of GBS data in vaccine-vigilance.⁸⁹ This definition contains three levels of diagnostic certainty classification. However, most studies on GBS incidence published before that date used the diagnostic criteria established by the National Institutes of Neurological and Communicative Disorders and Stroke (NINCDS).⁹⁰⁻⁹⁵

It should be noted that the NINCDS criteria do not include the symptoms of the Miller-Fischer syndrome, which is a subtype of GBS disease, while this syndrome is included in the BC definition.⁹⁶

5.3.3 Literature review

A literature review performed in 2009 for the KCE project Plasma, with search date up to December 2008, has been updated.

The inclusion criteria were studies from Western Europe, published between 01 Jan 2000 and 01 April 2012, and population based. Included languages were English, French and Spanish. The exclusion criteria included specific risk groups, clinical trials, study population <1 000 000, study period before 1995 (or separate rates for the period after 1990 are not provided), no diagnostic criteria described, study measuring the association between vaccines and GBS unless background incidence are used. A number of 77 articles were retrieved and 10 studies met the selection criteria.



5.3.4 *Background rates of Guillain-Barré Syndrome in the literature*

Two systematic reviews of GBS incidence published in 2009 and 2011 were retrieved.^{87,96} A first review retrieved 63 relevant studies on GBS incidence rates published between 1980 and 2008, but it included all articles irrespective of methodology and the majority of studies were old, covering periods before 1995.⁹⁶ Among the 10 selected studies estimating incidence in children (≤ 15 years), only one was published in Europe (Finland) and covers older periods (1980-86). The review retrieved 29 studies involving overall GBS incidence in Europe, and their incidence ranged between 0.84 and 1.89/100 000/year. However, only 12 studies cover periods from 1995 onward, and 6 of these do not fit with our selection criteria (no diagnostic criteria, published before 2000, study population $< 1\,000\,000$ or rates not stratified for period > 1995). The remaining 6 studies had been retrieved by our search and are described below in Table 11, together with more recent studies. A second review, published by the CDC, searched studies published up to December 2009 and used stricter selection criteria based on study design, diagnostic criteria and validation.⁸⁷ Additionally, it restricted the review to studies from Europe and North America and the studies based on ICD codes without validation of diagnosis were excluded. Overall, 16 relevant studies were retrieved and 13 studies were included in the meta-analysis. Out of these studies, 5 fitted our selection criteria and had been retrieved by the previous review and by our search (Table 11). The reported crude incidence ranged from 0.81 to 1.89/100 000 person-year. Data were also used to fit a regression model to predict age-specific incidence rates (see below).



Table 11 – Rates of Guillain-Barré Syndrome per 100 000 inhabitants from published studies

Study/country/period	Design/ study population	Rates per 100 000 (95% CI)	Case definition	Additional information
The Netherlands, 1996-2008 ⁸⁸	Retrospective review of GP database, population 1 MIO and 2.32 MIO person-years.	Crude: 1.14 (0.67-1.61) Adjusted for undocumented cases: 1.49	BC case definition	Two step validation for BC classification; 30% of cases could not be validated.
Germany, 2003-05 ⁹⁷	Retrospective review of hospital nationwide database (DRG-ICD), population 82 MIO.	Crude : 1.75	ICD-10 code G61.0	Based on hospital coding only, no validation of diagnoses
Italy, 1996 ⁹¹	Prospective, Lombardy hospital records.	Crude: 1.55 (1.30-1.83) Age- and sex-adjusted: 1.58 (1.48-1.69)	NINCDS criteria	
Spain, 1998-99 ⁹⁴	Prospective surveillance by a sentinel network of neurologists. Population 3.9 MIO, adults >19 years only.	Crude: 1.25 Age-adjusted: 1.26	NINCDS criteria	Validation of diagnoses by a neurologist
Spain, 1985-97 ⁹³	Retrospective review of records from hospitals, outpatient and neuro-physiological labs. Network of neurologists, 11 hospitals. Population 4 MIO, adults >19 years.	Crude: 1.01a	NINCDS criteria	Clinical records reviewed by a neurologist
Sweden (13 regions), 1996 ⁹⁸	Network neurologists, adults hospitalized + outpatient. Population 4.5 MIO	Crude 1.63 (1.28-2.05) Age-adjusted (EU): 1.51 (1.18-1.90)	NINCDS criteria	3% outpatient (non hospitalized)
Italy (2 regions: Piemonte and Valle d'Aosta), 1995-96 ⁹²	Prospective notification of neurology departments and search in hospital discharge data. Population 4 MIO	Crude: 1.36 (1.13-1.63) Age-adjusted: 1.32 (1.17-1.58)	NINCDS criteria	Validation: Review of clinical records by blinded experts. 5.8% GBS were outpatient

^a Recalculated on this study period based on data provided in tables

BC: Brighton Collaboration

NINCDS: National Institutes of Neurological and Communicative Disorders and Stroke

MIO: million

Our search retrieved 7 primary epidemiological studies conducted in the period 1995-2008, from Germany, Italy (2 studies), Spain (2 studies), Sweden and the Netherlands (Table 11), including a recent one that was not included in the two reviews.⁸⁸ One was based on GP records, four on hospital cases and the last two used multiple data sources. These studies reported relatively similar rates, in spite of different study designs, especially after adjustment. The crude incidence rate (all ages) ranged 1.01-1.75/100 000/year and incidence rates adjusted for age and/or sex and/or undocumented cases were slightly higher and ranged 1.26-1.58/100 000/year. This suggests that GBS occur relatively evenly, at least throughout Western Europe.

In all studies, rates were higher in males than in females and higher in adults than in pediatric ages. Incidence rose with increasing age - exponentially according to the meta-analysis of 13 studies.^{87,96} Some studies also showed that GBS declined with age after 70-80 years.⁹³⁻⁹⁵ The Sejvar review fitted a regression model including age to the data of 1643 GBS cases to estimate age-specific GBS incidence. Based on this model, the age-specific GBS rate increased from 0.62 cases/100 000 person-years in the <10 years to 2.66/100 000 person-years among the 80-89 year olds.⁸⁷

These studies also revealed interesting findings on the validity of the databases for GBS rates. Rates based solely on hospital discharges without validation of diagnosis were shown to substantially over-estimate disease incidence.²⁴ In Italy, Bogliu found a positive predictive value (PPV) of 54.8% of hospital discharge diagnosis, which was higher when databases were restricted to neurology wards.²⁴ Van der Maas found a PPV of 49% for manual review of GP electronic records, and only 6/23 incident cases fulfilled the level 1 or 2 of diagnostic certainty of the BC case definition.⁸⁸ The low PPV of medical records indicate that additional information needs to be collected, preferably by chart review in the hospital, as rates based on non validated cases may lead to overestimation and reduce the usefulness of these rates for observed vs. expected analysis.^{88,96}

5.3.5 Seasonal or temporal patterns

Most recent studies covering several years showed that the incidence of GBS is stable over time.^{88,99} This is important as it allows historic rates to be used for the calculation of the expected number of cases.⁸⁸

Overall, no clear or consistent seasonal pattern has been identified.^{88,96,100} However, many studies reported highest rates in spring,^{88,92,93,99} while some described higher rates in winter.^{91,94} Lowest rates were also reported in summer.^{88,94}

5.3.6 Prediction models

Two Spanish studies conducted by the same author describe models to predict incidences and establish thresholds for signal detection. Cuadrado used a Poisson model on retrospective data to predict monthly incidences; predictions by an autoregressive integrated moving average (ARIMA) model were rejected due to the lack of normality and white noise of the series.⁹³ The thresholds were later recalculated by adding prospective data later collected.⁹⁴

Based on a meta-analysis, Sejvar derived an equation to calculate an average GBS rate as a function of age in years, with a single random effect for the slope parameter.⁸⁷ In this study, the negative binomial model fitted the data better than the Poisson model.

5.3.7 Belgian data on GBS from Minimal Clinical Data

GBS data from the MCD dataset with ICD-9 code 357.0 are described below and more details are provided under section 7.1. These data are based on the minimal data sent by the hospitals on each hospitalized patient, and no diagnostic validation is performed.

In average, 550 annual GBS hospitalizations have been reported over 2004-09, including 55% hospitalizations for GBS as principal diagnosis. Duplicate admissions (referral to another hospital or re-admissions) are reported in 25% of all GBS admissions (any diagnosis), amounting to 18% among admissions for GBS admissions as principal diagnosis. When excluding duplicate admissions, the crude GBS rate ranges 2.2-2.4 per 100 000 for principal diagnosis and 3.9-5.0 per 100 000 for any diagnosis (Figure 8). Crude rates for GBS as principal diagnosis are stable across the years.

Figure 8 – Incidence rates (crude) of hospitalized Guillain-Barré Syndrome cases (ICD-9 code 357.0) based on MCD over the period 2000-07, by diagnosis

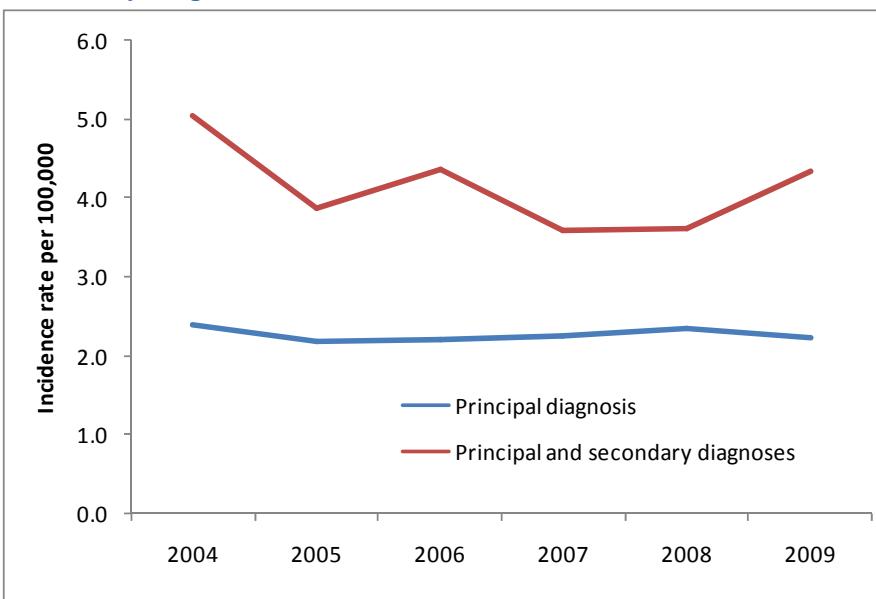


Table 12, based on principal and secondary diagnosis over 2000-07, shows that the mean hospitalization rate increases with increasing age. Corresponding annual hospitalization rates in children (0-18 years) ranged 1.0-2.2/100 000 and rates in adults (≥ 18 years) ranged 6.9-8.5/100 000 across the period.

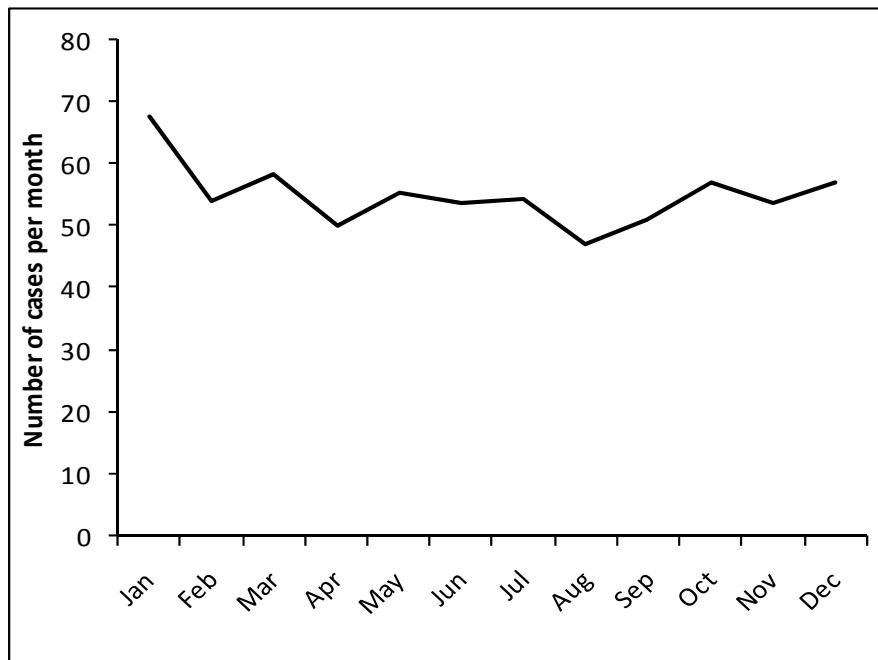
Table 12 – Hospitalized Guillain-Barré Syndrome cases based on MCD by age group, any diagnosis, over the period 2000-07

	N cases	Rates per 100 000
0-9 years	21	1.74
10-19 years	22	1.76
20-29 years	34	2.63
30-39 years	60	3.96
40-49 years	77	4.93
50-59 years	109	8.25
60-69 years	121	11.99
70-79 years	139	16.28
≥ 80 years	78	18.15
Total	660	6.34

MCD: Minimal Clinical Data

Rates per month show no clear seasonality (principal and secondary diagnoses, Figure 9). Numbers in January are slightly higher but may also represent post-holiday catch up in admissions (or re-admissions after Christmas break).

Figure 9 – Monthly number of hospitalizations for Guillain-Barré Syndrome per month, Minimal Clinical Data, mean over 2000-07, Belgium



The rates for GBS as principal diagnosis are higher than the range of rates published in other EU countries (1.01-1.75, see Table 11). A major difference is that most published studies had their GBS cases validated by experts, while MCD diagnoses were not validated, and it has been shown that rates based solely on hospital discharges without validation of diagnosis substantially tend to over-estimate disease incidence.^{24,88,96} The proportion of duplicate admissions in the Belgian MCD compares with the proportion found in an Italian study (Lombardy) where 29% of the 361 hospital discharge diagnoses ICD-9 357.0 were re-admissions of the same patients for GBS.²⁴

Two other factors need to be taken into account when interpreting these data:

- A number of chronic neurological diseases may display similar signs and symptoms in a first phase (e.g. chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN)). These diseases may thus first be diagnosed as GBS at their first occurrence. A former KCE report on plasma derivatives show that an estimated 150 new GBS cases would occur in Belgium each year based on rates from the literature, but there is an estimated total of 340 cases of MMN and CIDP in Belgium. An Italian study found that 21% of hospital discharge diagnoses for GBS had chronic neurological diseases, and only 38% of all cases fulfilled the diagnostic criteria for typical or atypical GBS.²⁴
- Immunoglobulins (Ig), that are reimbursed in case of GBS with specific criteria, may show benefit for a variety of chronic demyelinating neurological diseases but are not reimbursed for most of these conditions. As Ig are very expensive and difficult to purchase, it is possible that other demyelinating diseases are labeled as GBS at hospital level to allow access to (free-of-charge) Ig for these patients.

5.3.8 Conclusions on Guillain-Barré syndrome (GBS)

The literature review showed relatively homogenous background rates of GBS across Western Europe countries, based on 7 selected studies. The crude annual incidence rate for all ages ranged 1.01-1.75/100 000 and 1.26-1.58/100 000 when rates were adjusted for age and/or sex and/or undocumented cases. Belgian inpatient data based on MCD show slightly higher rates at around 2.0 per 100 000 but diagnoses are not validated. Other studies have shown that rates based on hospital discharge data over-estimate true GBS rates due to the inclusion of other cases. Additionally, the potential for misclassification of chronic neurological diseases at first admission and reimbursement rules for immunoglobulins may inflate the number of admissions coded as GBS in Belgium. As the diagnosis of GBS safety signals are expected to be validated, the estimation of background rates based on literature review and regularly updated is likely to be a best and relatively robust option than MCD data. However, signals based on unvalidated (or not yet validated) GBS cases could be compared with rates based on Belgian MCD data.



5.4 Seizures

5.4.1 Case definition

The Seizure Working Group from the Brighton collaboration focused on a definition of generalized convulsive seizures, as they represent the majority of childhood seizures independent of immunization. They did not define febrile seizures separately, as fever is rarely measured prior to the seizures and temperatures measured after the seizure are often altered by antipyretics.

Therefore they retained as a case definition of generalized convulsive seizure as an adverse event following immunization:

- Level 1 of diagnostic certainty: witnessed sudden loss of consciousness AND generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations,
- Level 2 of diagnostic certainty: history of unconsciousness AND generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations,
- Level 3 of diagnostic certainty: history of unconsciousness AND other generalized motor manifestations.

Although the option taken by the Brighton collaboration is certainly the most realistic option for the purposes of a uniform and reproducible data collection, it makes the comparison with published incidence rates difficult, as epileptic seizures and febrile seizures are usually reported as a separate categories in separate publication for different age groups, making the interpretation of published rates difficult and limiting its use in e.g. an O/E analysis.

5.4.2 Literature review

We searched medline (OVID), on both the mesh terms “Seizures” and “Febrile seizures” combined with the terms “epidemiology” or “incidence”. We did not apply other restrictions such as country, language or date. We also scanned selected publications for additional references.

A total of 1485 articles were retrieved and after examination of title and abstract, 16 publications were examined in full text. Eight publications concerning 7 studies met the selection criteria. Publications excluded after full text examination and the reasons for their exclusion on full text are listed in Table 13.

Table 13 – Literature search on convulsions - Excluded studies and reasons for their exclusion

Study reference	Reason for exclusion
Alper et al, 2007 ¹⁰¹	Patients with psychiatric disorders
Kelly et al, 2010 ¹⁰²	No incidence rates reported
Klein et al, 2010 ¹⁰³	Only relative risks reported
Miller et al, 2007 ¹⁰⁴	Only relative risks and risk per 10 000 doses reported
Stehr-Green et al, 2008 ¹⁰⁵	Only excess risk reported
Sun et al, 2012 ¹⁰⁶	Survival analysis, only Hazard rates reported
Svanström et al, 2010 ¹⁰⁷	No interpretable baseline incidence provided
Vahidnia et al, 2008 ¹⁰⁸	Survival analysis, only Hazard rates reported

5.4.3 Results

Very few publications have as primary purpose the estimations of incidence rate of seizures, but provide information as part of a study on risk factors for seizures. Unfortunately a lot of studies report hazard ratio's and could not be used.

Hauser et al.¹⁰⁹ reviewed incidence rates of provoked and unprovoked seizures in the literature, excluding febrile seizures however, limiting its use as a background rate for vaccination related seizures. They found rates varying from 70.8/100 000 population per year to 100/100 000 population per year but it is unclear how this could be used for signal detection or evaluation.

Cordato et al.¹¹⁰ measured only seizures presenting at emergency departments in Australia and found an incidence of 248/100 000 population per year (all ages). Polkinghorne et al.¹¹¹ examined and found a relationship between the population incidence of febrile convulsions in young children in Sydney, Australia and seasonal epidemics of influenza and respiratory syncytial virus. They reported incidences among children aged < 6 years of 819/100 000 population per year according to the provisional emergency department diagnosis and 583/100 000 population per year according to emergency ambulance dispatches.

Vestergaard et al.¹¹² reviewed the information on febrile seizures coming from the Danish registers, they only reported cumulative incidence at year 5. In another publication, when comparing the register with a cohort study, they found that these registers had a completeness of around 70%.¹¹³

Hamdy et al.¹¹⁴ found an all seizure rate among under fives of 357/100 000 population per year in Bradford, UK, an industrial town. He found large racial discrepancies, with a rate of 284/100 000 population per year among the white population and of 543/100 000 population per year in the south Asian population, predominantly due to differences in the rate of febrile seizures.

Silanpaa et al.^{115,116} measured incidence of febrile seizures prospectively determined in a cohort study until they reach the age of 5 years and found a cumulative incidence of 6.9% with a yearly incidence of 1400/100 000. They found also that retrospectively collected data found a lower incidence (5.7%), indicating that the way incidence is measured has important implications.

Shui et al.¹¹⁷ assessed the positive predictive value (PPV) of ICD-9 codes in children from 6 weeks to 23 months who were enrolled in seven managed care organizations in the US and found that the PPV of ICD-9 codes was highest in the setting (97%), followed by the inpatient setting (64%). In the outpatient setting, computerized codes for seizures had very low PPV: 16% on days 1–30 following vaccination and 2% for visits on the same day of vaccination. An estimated 77% of true seizures identified were from the emergency department or inpatient settings. This implies that estimating febrile seizures from hospital based data such as the MCD data may provide useful background rates even if the primary care setting is not taken into account.

VAESCO reported incidences among under fives ranging from 447/100 000 person years to 1441/100 000 person years in Denmark. Also incidence rates in person above 10 years old vary wildly, from 48/100 000 person years in Spain to 378/100 000 person years in Finland. This variations reflect probably huge differences in data collection systems, case definitions and genuine variability, despite the efforts of VAESCO to standardize those.

Table 14 – Incidence rates for seizures, febrile or afebrile, per 100 000 inhabitants from published studies

Study / country / period	Design / study population	Rates per 100 000 (95% CI)	Case definition	Additional information
Australia ¹¹¹	Provisional emergency department diagnosis in 35 hospitals in Sydney and emergency ambulance dispatches	Period 1 January 2003 to 30 April 2010 in aged < 6 years old: average incidence of 819/100 000 population per year according to the provisional emergency department diagnosis. Period 1 July 2006 to 30 April 2010 in children < 6 years: average incidence rate of 583/100 000 population per year according emergency ambulance dispatches	Provisional unconfirmed	Relation with influenza and respiratory syncytial virus (RSV) seasonal epidemics
France ¹⁰⁹	Prospective cohort study	71.3/100 000 population per year	Acute symptomatic seizures and unprovoked seizures	Afebrile
US ¹⁰⁹	Retrospective cohort	100.0/100 000 population per year	Acute symptomatic seizures and unprovoked seizures	Afebrile
Sweden ¹⁰⁹	Prospective cohort study	76.0/100 000 population per year	Acute symptomatic seizures and unprovoked seizures	Afebrile
Switzerland ¹⁰⁹	Prospective cohort study	70.8/100 000 population per year	Acute symptomatic seizures and unprovoked seizures	Afebrile
Denmark ¹¹²	Register based	Cumulative incidence at age 5 3.9% Peak between 10 and 20 months	Febrile seizures	No yearly incidences given
Australia ¹¹⁰	Register based	248/100 000 population per year (all ages)	All seizure	Only seizures presenting at emergency departments.
UK ¹¹⁴	Register based, pediatric services UK	284/100 000 population per year at age 5	All seizure	Bradford, large ethnic discrepancies found
Finland ^{115,116}	Prospective cohort study	Cumulative incidence at age 5 6.9% Peak between 10 and 20 months	Febrile seizure	Lower in retrospective cohort
UK ^{118,119}	Prospective cohort study	Cumulative incidence at age 5 2.3% Peak between 10 and 20 months	Febrile seizure	



5.4.4 Belgian data

5.4.4.1 Intego

Intego, the GP database from the University of Leuven, reported incidences among under fives of 92/100 000 persons per year for women and 99/100 000 persons per year for men in the period 2008 – 2010 and incidences for all age groups of 9/100 000 persons per year for women and 14/100 000 persons per year for men. These lower rates probably reflect the fact that most cases of seizures do not come in contact with a GP in Belgium leading to an underestimation.

5.4.4.2 Minimal Clinical Data

See below: 7.2 seizures.

5.4.5 Discussion

Apart from the VAESCO project, no studies examined the incidence of seizures specifically with the purpose of providing background rates to evaluate vaccine safety. Case definitions, sources and data collection methods varied a lot in the studies, and most measured either febrile seizures or non febrile seizures. Moreover, due to the fact that febrile convulsions are shown to be linked to epidemics of flu or other diseases causing fever and the fact that it seems to be linked to social, ethnic and behavioral variables there are indications that there are also considerable regional and temporal variation. Also the estimations provided by the VAESCO project vary rather wildly, more than can be expected on epidemiological grounds only but reflecting differences in the data collection systems, this despite the fact that the stated objective was to come to a harmonized system. All these elements make it unlikely that data from the literature on convolution are useful for signal detection and evaluation of the link between convulsions and vaccination using background rates for O/E assessment. The attributable rate, this is the rate of convolution that can be attributed to vaccination is low, especially when the definitions from the Brighton collaboration are used, making signal detection difficult.

6 POTENTIAL DETECTION OF CASES OF SD/SID, GBS, THROMBOCYTOPENIA AND CONVULSIONS FROM IMMUNOGLOBULIN'S PRESCRIPTIONS

The list of polyvalent immunoglobulin's licensed and entitled to reimbursement in Belgium was found on the Centre Belge d'Information Pharmacothérapeutique / Belgisch Centrum voor Farmacotherapeutische Informatie (CBIP/BCFI). The ATC code J06BA (Immunoglobulins, normal human) was used. This code is further divided into J06BA01 (immunoglobulins, normal human, for extravascular administration) and J06BA02 (Immunoglobulins, normal human, for intravascular administration).

The database of reimbursed pharmaceuticals from the National Institute for Health and Disability Insurance (NIHDI) website was then consulted to retrieve the reimbursement conditions of each immunoglobulin. Table 15 contains the brand names of the immunoglobulins licensed in Belgium together with their specific reimbursement criteria.



Table 15 – List of the immunoglobulins licensed in Belgium

Name	Firm	Reimbursement conditions
ATC CODE : J06BA01 - Immunoglobulins, normal human, for extravascular administration		
Gammanorm	Octapharma	Chapter IV - §3 410 000
Hizentra	CSL Behring	Chapter IV - §3 410 000
Subcuvia	Baxter	Chapter IV - §3 410 000
Vivaglobin	CSL Behring	Chapter IV - §3 410 000
ATC CODE : J06BA02 - Immunoglobulins, normal human, for intravascular administration		
Gammagard	Baxter	Chapter IV - §90 000
Sandoglobuline	CSL Behring	Chapter IV - §3 190 000
Multigam	C.A.F. - D.C.F.	Chapter IV - §3 200 000
Kiovig	Baxter	Chapter IV - §3 210 000
Nanogam	C.A.F. - D.C.F.	Chapter IV - §3 210 000
Octagam	Octapharma	Chapter IV - §3 210 000
Privigen	CSL Behring	Chapter IV - §3 210 000

Immunoglobulin's are reimbursed according to Chapter IV of the list of reimbursed pharmaceuticals. Reimbursement of such pharmaceuticals is subject to particular reimbursement conditions, which are imposed for medical and/or budgetary reasons. These conditions (e.g. a selection of therapeutic indications) are set out in the corresponding paragraph. Moreover, reimbursement requires prior authorization by the medical officer ("médecin conseil / adviserend geneesheer") of the patient's insurance institution, in case the patient meets these conditions: the so-called "a priori" control.

The prescribing physician must introduce the request to obtain the agreement for reimbursement. For immunoglobulin's from ATC code J06BA01, a "non-specific" form must be filled (see Appendix 4). For immunoglubilin's from ATC code J06BA02, there is no predetermined form. The physician must thus prepare a "dossier" justifying that the conditions defined in Chapter IV are met.

6.1 Immunoglobulins for extravascular administration (J06BA01)

According to Chapter IV §3 410 000 of the list of reimbursed pharmaceuticals, these immunoglobulins are reimbursable for the following conditions only: "Syndromes d'immunodéficience primaires and Myélome et leucémie lymphoïde chronique avec hypogammaglobulinémie secondaire sévère et infections récidivantes". The legal text in full is to be found in Appendix 5. None of the 4 specific conditions studied here can thus be identified via the prescriptions of this type of immunoglobulin's.

6.2 Immunoglobulins for intravascular administration (J06BA02)

The full reimbursement criteria (in terms of specific indications) for this type of immunoglobulins are listed in Appendix 6. Among others, immunoglobulins for intravascular administration can be prescribed and reimbursed for the two following conditions of interest for our purpose:

Idiopatische trombocytopenische purpura:

- bij kinderen;
- bij volwassenen met een hoog risico op bloedingen of die wachten op een nakende heelkundige ingreep.

Syndroom van **Guillain-Barré** bij patiënten met één van de volgende symptomen:

- progressieve parese (de patiënt kan niet meer dan 10 meter onafhankelijk lopen);
- aanwijzingen van een respiratoire aandoening (klinische observatie of aangetoond door meting van de vitale capaciteit aan het bed van de patiënt);
- tekens van bucco-faryngeale parese.

Cases of thrombocytopenia and Guillain-Barré syndrome could thus theoretically be identified by regularly consulting the reimbursement request files for immunoglobulins kept by the medical officer of each insurance institution in Belgium.

However, the cases identified with this procedure would only represent the most severe cases of thrombocytopenia and Guillain-Barré syndrome,

given the stringent reimbursement criteria. The interest for our purpose is thus rather limited. Another way of finding Guillain-Barré syndrome in administrative data (coupled IMA and MCD data) would be to identify codes for a combination of immunoglobulin prescription and diagnostic procedure (lumbar puncture + electromyogramme + neurological consult). The feasibility and validity of such procedure was however not tested in this report.



7 MINIMAL CLINICAL DATA

We tried to estimate the incidence of a number of conditions that could serve as a background rate. The objective was to explore the problems and biases that are encountered during this effort. We compared the results with the results from the VAESCO project. We based the choice of the disease codes on the ICD-9-CM disease codes used in the VAESCO project. An ICD-9-CM Code searching application developed by KCE (Stefaan Van de Sande) was used to adapt the codes for diagnosis, including uptake of 4-digit level ('parent') and 3-digit level ('grandparent') codes. Code history was recorded, codes were exported to an excel file. Post search processing was performed, the final decision on what codes to include was guided by the case definitions of the Brighton collaboration <https://brightoncollaboration.org> and the Belgian ICD-9-CM Code handbook version 2009.

For the syndromes with a long duration, in casu demyelinating disease, Guillain-Barré syndrome, Optic neuritis and Bell's palsy, we used the unique patient identifier to try to wield out the doubles, only counting the first entry from the period 2004-2009 as incident case. Note that, as for 2004 no ID numbers are available, we could not identify all second admissions. For diseases with a short duration, such as an admission for convulsions or thrombocytopenia where it can be assumed that they occur more in attacks, we did not wield out doubles. Another important issue is the distinction between admission as principal diagnosis and secondary diagnosis. Here we opted to make a justified choice depending on the disease, the choice is justified per disease on which we reported.

We also report the number of doubles that we eliminated in this way. We present crude incidence (with the Belgian population of the year concerned as denominator) and age standardized rates by direct standardization using the WHO world population as a standard (we choose the same standard as the VAESCO project does to ensure comparability, but other choices could have been justified).

7.1 Guillain-Barré syndrome

MCD data make a distinction between principal or secondary diagnosis. It is not clear what the real implications are when trying to estimate the incidence of GBS. It may be reasonable to assume that for the hospitalization of a first occurrence of GBS the latter would be the main diagnosis, but this is not sure. We report therefore both estimations of the incidence based on admission with GBS as principal diagnosis and estimations using both admissions with GBS as principal or as secondary diagnosis.



Table 16 – Number of admissions with GBS as principal diagnosis, double admissions and admissions without ID number, crude incidence and age standardized incidence (per 100 000 person years) for the years 2004 - 2009

Year	Double	First entry with ID number available	Entry without ID number	TOTAL	Crude Incidence	Age standardized incidence
2004	68	246	18	332	2.40	2.06
2005	61	225	22	308	2.18	1.93
2006	73	229	18	320	2.21	1.95
2007	55	235	13	303	2.26	1.97
2008	50	245	12	307	2.35	1.91
2009	16	233	10	259	2.22	1.88
TOTAL	323	1413	93	1829		

Table 17 – Number of admissions with GBS as principal and secondary diagnosis, double admissions and admissions without ID number, crude incidence (per 100 000 person years) and age standardized incidence for the years 2004 - 2009

Year	Double	First entry with ID number available	Entry without ID number	TOTAL	Crude Incidence	Age standardized incidence
2004	159	460	36	655	5.04	4.82
2005	182	356	39	577	3.87	4.15
2006	117	403	34	554	4.36	4.09
2007	151	333	33	517	3.59	3.72
2008	153	337	23	513	3.61	3.50
2009	72	407	29	508	4.33	3.49
TOTAL	834	2296	194	3324		



The data show a slight decline in incidence. This may be an artifact, however, due to the fact that in the earlier years we could not detect second admissions of patients diagnosed before 2004. Incidence rates, when only principal diagnoses are taken into account, are slightly higher than those reported in the literature. The reasons could be undetected secondary admissions, reporting of related conditions for which immunoglobulin is needed and that are only reimbursed if a label of GBS is given. The data are grossly comparable to the data from the VAESCO project, where the lack of case ascertainment probably also leads to over-reporting.

Table 18 – Number of admissions with seizures (Brighton definition), crude incidence (per 100 000 person years) and age standardized incidence for the years 2004 - 2009

Year	Number of admissions	Crude Incidence	Age standardized incidence
2004	12236	119.22	120.06
2005	12172	118.06	119.99
2006	12072	116.57	117.55
2007	12757	122.71	122.79
2008	12047	115.33	118.08
2009	11573	110.1	112.84
TOTAL	72857		

The estimations fall grossly within the range of values reported by the VAESCO project. However, estimations between countries vary rather wildly so it is difficult to know if the estimation coming from the MCD data is correct. An increase in incidence due to events related to vaccination may be difficult to detect if based on all seizures, as seizures linked to vaccination are likely to be febrile, being only a minor part of the seizures reported in this way. It is difficult to compare the estimations with estimations from the literature, as type of seizures and reported collection methods differ too much.

7.2 Seizures.

Following the Brighton criteria, the VAESCO project used a broad definition of seizures, not limited to febrile seizures but also including epileptic seizures and related conditions. In order to see what the result is when you apply this to the Belgian MCD data, we used the same codes that VAESCO used, but we gave also a second estimation only measuring febrile seizures.

Table 19 – Number of admissions with febrile seizures, crude incidence (per 100 000 person years) and age standardized incidence for the years 2004 - 2009

Year	Number of admissions	Crude Incidence	Age standardized incidence	Number of admissions amongst 0 – 4 year old	Crude incidence among 0 - 4 year old	Number of admissions among < 1 year old	Crude incidence among < 1 year old	Number of admissions among 1 year old	Crude incidence among 1 year old
2004	809	7.9	12.3	739	128.0	164	278	273	469
2005	867	8.4	13.2	788	136.9	165	283	292	492
2006	924	8.9	14.0	728	127.1	133	231	276	471
2007	942	9.1	14.5	862	150.9	180	311	290	501
2008	1020	9.8	15.6	944	164.2	307	510	327	560
2009	890	8.5	13.5	807	139.0	207	337	297	489
TOTAL	809	7.9	12.3	739		164	278	273	469

In the literature cumulative incidences for under fives are reported ranging from 2 to 5%. The estimations from MCD are considerably less than that, maybe because not all febrile seizures are hospitalized or because seizures are not declared if patient is hospitalized for other reasons, such as pneumonia. As reported in the literature, incidence of febrile seizures peaks among one-year olds.

7.3 Demyelinating disease

Codes of VAESCO were used to estimate the incidence of demyelinating disease in the MCD data. Estimations are comparable though some 20 to 25% higher than the rates reported in the VAESCO project for most countries (but between country estimations differ widely). Note the high proportion of doubles identified. This indicates that an overestimation may exist for doubles as we can certainly not identify all re-admissions with the information available.

Table 20 – Number of admissions with demyelinating disease as principal diagnosis, double admissions and admissions without ID number, crude incidence (per 100 000 person years) and age standardized incidence for the years 2004 - 2009

Year	Double	First entry with ID number available	Entry without ID number	TOTAL	Crude Incidence	Age standardized incidence
2004	1172	1097	285	1172	13.47	11.60
2005	1262	990	244	1262	11.97	10.15
2006	1233	959	202	1233	11.21	9.49
2007	910	1052	215	910	12.21	10.50
2008	723	1207	226	723	13.71	11.81
2009	910	1187	172	910	12.92	10.91
TOTAL	6210	6492	1344	6210		

7.4 Optic neuritis

Table 21 – Number of admissions of optic neuritis, double admissions and admissions without ID number, crude incidence (per 100 000 person years) and age standardized incidence for the years 2004 - 2009

Year	Double	First entry with ID number available	Entry without ID number	TOTAL	Crude Incidence	Age standardized incidence
2004	9	103	9	121	1.14	1.16
2005	6	96	9	111	1.08	1.08
2006	3	109	4	116	1.09	1.05
2007	7	99	4	110	1.04	1.03
2008	2	105	5	112	1.06	1.06
2009	7	104	2	113	0.92	0.89
TOTAL	34	616	33	683		



7.5 Bell's palsy

Table 22 – Number of admissions of Bell's palsy, double admissions and admissions without ID number, crude incidence (per 100 000 person years) and age standardized incidence for the years 2004 - 2009

Year	Double	First entry with ID number available	Entry without ID number	TOTAL	Crude Incidence	Age standardized incidence
2004	24	329	25	378	3.68	3.09
2005	15	300	25	340	3.41	2.88
2006	13	290	20	323	3.19	2.73
2007	8	320	18	346	3.42	2.87
2008	9	280	21	310	3.05	2.57
2009	11	309	17	337	3.34	2.87
TOTAL	80	1828	126	2034		

Estimations are considerably lower than the estimation VAESCO provided.
The most likely explanation is the fact that a considerable proportion of patients suffering from Bell's palsy are not hospitalized and therefore not included in the MCD data.



7.6 Thrombocytopenia

Table 23 – Number of admissions with thrombocytopenia, crude incidence (per 100 000 person years) and age standardized incidence for the years 2004 - 2009

Year	Number admissions	of	Crude Incidence	Age standardized incidence
2004	12280		119.6	85.6
2005	12891		125.0	89.6
2006	10497		101.4	71.5
2007	13743		132.2	94.4
2008	13569		129.9	93.4
2009	11982		114.0	79.0
TOTAL	12280		119.6	85.6

Crude and age standardized number of hospitalizations per year is somewhat higher than most estimations from VAESCO. Interpretation of the data on thrombocytopenia is difficult because of the diversity of the conditions where thrombocytopenia occurs, the definition from the Brighton collaboration included again all forms of thrombocytopenia. The MCD data on the more idiopathic thrombocytopenic purpura are very instable and difficult to interpret. There only seems to be a limited number of cases reported for the year 2009. This is probably due to coding and interpretation of the case definition.

7.7 General discussion on MCD data

We only examined a selected number of conditions in order to highlight lessons to be learned and to warn to be cautious in the interpretation of MCD data when trying to estimate the background incidence of a potential vaccine related adverse effect. MCD data are not in the first place meant to be used for epidemiological purposes, so one should be very cautious when giving an interpretation of the data.

Biases differ strongly per condition and depend on:

- Duration of the condition. Long lasting conditions that require multiple hospitalizations will be overestimated, as repeat hospitalizations can only be partially detected. This is because unique patient identifiers are only available from 2004 on. Number of repeat hospitalizations varies from less than 5% to 50%, as is e.g. the case for demyelinating disease.
- The MCD data make a distinction between a principal diagnosis and secondary diagnosis. How this information must be used however is uncertain and depends on the condition you want to measure. For a severe and chronic condition such GBS or demyelinating disease, it can maybe be assumed that during the first hospitalization for this condition, it would be labeled as primary diagnosis and as secondary diagnosis if the patient was hospitalized for another condition while still suffering from the same condition. This is not an absolute rule however, making interpretation difficult.
- Only hospitalized cases end up in the database, so less severe cases will not be reported. Although one can object that only severe cases are important, deciding on severity introduces subjective and context-specific elements that add to the variability and uncertainty that surround the estimations.



Some of the estimations seem plausible when compared to the international literature and the data from the VAESCO project. Others lack credibility and are clearly biased. Unfortunately, even for the estimations that are plausible, we cannot exclude that this is a mere coincidence. This strongly limits the usefulness of these estimations. Moreover, for most conditions, especially the more common ones such as thrombocytopenia, the attributable risk due to vaccination is low as there are important other causes for the disease, limiting the power of signal detection in these cases.

8 PHARMACOVIGILANCE IN BELGIUM

The pharmacovigilance in Belgium is the legal responsibility of the division vigilance of the FAMHP, which is an agency under the Ministry of Health.

8.1 Data collection

The FAMHP receives both individual reports and compilation of data concerning the adverse effects of medicines.

- *Individual reports* include “yellow cards” from health care professionals (doctors, pharmacists, dentists, nurses, midwives) and individual case reports from marketing authorization holders. Patients are also able to report adverse drug reactions directly to the FAMHP (an online pdf form is available). Furthermore, promoters of clinical trials are also required to submit all SUSARs (Suspected Unexpected Serious Adverse Reactions) that occurred during their clinical trial, both for medicines with and without marketing authorization. All these individual case reports are submitted electronically to and collated into the EudraVigilance database. This central repository, held at the EMA, contains reports of suspected adverse reactions related to medicines authorised in the European Economic Area and medicines being studied in clinical trials. Competent authorities have access to all individual case safety reports (ICSR) data elements in EudraVigilance.
- *Compilation of safety data* is regularly sent by marketing authorization holders (MAH) in forms of Periodic Safety Update Reports (PSURs). At regular intervals, they need to communicate an overview and an evaluation of all serious and non-serious reactions, that occurred inside and outside the European Union. After 5 years they must provide a global overview in the context of a marketing authorization renewal dossier. In order to evaluate the safety of the medicines used in clinical trials, the promoter must write a safety report each year about the serious adverse events that happened during a clinical trial and submit it to the FAMHP = ASR (Annual Safety Report). The MAH who are informed about a serious adverse effect, either by healthcare professionals, or by investigators of clinical trials, or by scientific publications, must report this to the FAMHP within 15 days of the receipt of the information for non interventional trials and within 7 days

for interventional trials. Non serious adverse events must be reported within 90 days.

Health care professionals are particularly encouraged to report in the following situations:

- **Serious adverse effects:** adverse effects that have led to hospitalization or prolongation of the hospitalization, that have been life-threatening, or that have caused death, permanent or significant disability or inability to work, or congenital disorder or malformation.
- **Unexpected adverse effects:** adverse effects of which the nature, the seriousness and/or the evolution do not correspond with what is mentioned in the Summary of Product Characteristics (SPC).
- **Suspected adverse effects:** adverse effects that are known but of which the frequency, the seriousness or the result is abnormal.

Particular situations:

- Vulnerable populations (e.g. children, pregnant or breastfeeding women, elderly, patients with hepatic or renal failure),
- Administration of vaccines,
- Switch from one specialty to another during treatment, regardless if it concerns the switch between “original” medicines, from a “generic” to an “original” medicine, from an “original” to a “generic” medicine or between “generic” medicines,
- Misuse and abuse of a medicine, medication errors and professional exposure to a medicine.

The FAMHP evaluates the individual reports of adverse effects (spontaneous reports and SUSARs) but also evaluates the summary reports (periodic safety reports concerning a medicine; annual safety reports concerning a clinical trial (in case of medicines disposing already of a marketing authorization); specific safety reports). For these tasks, the FAMHP is assisted by a team of internal and external experts. The individual reports are evaluated at regular intervals by a specific working group. The evaluation reports about periodic safety reports and the marketing authorization renewal dossiers are submitted to a second specific working group. In case of medicines for which the responsibility for the evaluation is at national level, it is the Commission for Medicines for

Human Use that gives the final advice about whether or not the measures suggested by the two working groups can be implemented. Based on the conclusions of these evaluations on national and European level, the BCPH takes the necessary measures.

We reviewed the data collected by the FAMHP in relation to vaccine since the year 2008.

Table 24 shows the number of suspected AEFIs reported to FAMHP per year since 2008 (2012 the period is only half a year). The annual count is around 200 reports per year. The peak in 2009 is mainly due to the reporting of side effects linked to Pandemrix, the vaccine used during the influenza pandemic.

Table 24 – Number of suspected adverse events following immunization reported to the BCPH since 2008 up to mid 2012

Year	Number	Percent
2008	216	20.95%
2009	352	34.15%
2010	170	16.50%
2011	208	20.20%
2012	85	8.20%
Total	1031	100.00%

The database includes a limited number of duplicates. Most frequent reports were on HPV vaccine (Gardasil, 214), difteria, pertussis, tetanos vaccine infanrix (132) and the vaccine against the 2009 pandemic influenza (93). A considerable part of reports contain more than one vaccine as well as other drugs, so it is not always clear to what (if any) vaccine the potential adverse events can be attributed.

For the description of the adverse event, MedDRA (Medical Dictionary for Regulatory Activities), a medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products is used. This dictionary comprises a mix of diagnosis and symptoms. How the diagnoses were determined is unknown, but it does not appear that specific definitions (e.g. Brighton classification) of the AEFIs were used. If and how the diagnoses were ascertained is unknown, but part of adverse events reported to BCPH were clearly not vaccine related, such as lung metastasis, bloody diarrhoea or secondary syphilis. Some reports even concern vaccine failures, storage problems and inadequate use. Exploiting these data is difficult and would require data mining. However, even in case of proper recoding, adequate diagnosis ascertainment and appropriate data mining, the number of reports is low with the current system, reducing the statistical power of any analysis.

To increase the number of reports of adverse effects of medicines, directly transmitted to the FAMHP by the healthcare professionals and to improve the quality of these reports, the « Active Pharmacovigilance » project was launched by the FAMHP in 2008. A communication announcing the project was published in the *Folia Pharmacotherapeutica* of January 2008 and a call for participation was published on the website of the FAMHP, CBIP/BCFI, several professional associations and the Medical Pharmaceutical committees. Within this project awareness sessions have been and will continue to be organized for universities, hospitals and medical/pharmaceutical associations. An online reporting tool has been made available, a more user-friendly paper version has been distributed via the *Folia Pharmacotherapeutica* since March 2009, a more detailed and individualized feedback is sent to the notifier in response to each report, and an electronic newsletter “VIG-news” containing recent pharmacovigilance news from different sources is available on the website of the FAMHP. In spite of these efforts, no upward trend is observed in the report numbers.

8.2 Data analysis

Currently, the FAMHP does not perform data analysis. All individual reports received by the FAMHP within the scope of the legislation of vigilance and clinical trials, are managed from the European Eudravigilance database of the EMA. Statistical analysis is done by EMA.

All serious paper reports directly received by the FAMHP, are submitted to the European Eudravigilance database as soon as possible, but at least within 14 days after the receipt of a report.

All non-serious paper reports that the FAMHP will receive directly within the scope of a new pharmacovigilance legislation, will be submitted to the European Eudravigilance database within 90 days after the receipt of a report.

The MAH and sponsors of clinical trials submit their own reports to the European database (http://www.fagg-afmps.be/nl/MENSELIJK_gebruik/geneesmiddelen/geneesmiddelen/genemeddelenbewaking/info_icssrs_mah_sponsors/).

The reporting criteria are the following: 7 days for a fatal report from an interventional clinical trial; 15 days for all other serious reports; 90 days for non-serious reports (from 2015). The FAMHP has direct access to all reports by its access to the European Eudravigilance database.

On a regular basis, the EMA performed data mining (PRR : Proportional Reporting Ratio)^m on the dataset Eudravigilance, and feeds results back to national agencies of pharmacovigilance. As per the new legislation, the FAMHP will have to analyse the Eudravigilance data provided by EMA (Excel data sheets: eRMR, Electronic Reaction Monitoring Reports) to perform the screening of new potential signals or to check whether a risk for a specific drug-event combination has changed.

^m The PRR is a measure of disproportionality of reporting of drug – event pairs used to detect signals of disproportionate reporting (SDRs) in pharmacovigilance databases such as EudraVigilance.



9 GENERAL DISCUSSION AND RECOMMENDATIONS

We have shown that it is possible to compute background rates of a number of health conditions in Belgium. Although the reliability of these background rates is not known with accuracy, it is likely to be fairly high for rates based on the principal diagnosis of clearly defined conditions requiring systematic hospitalization, or on the causes of death registered on death certificates. The current Belgian data collection system is too fragmented for computing reliable background rates of other health conditions.

However, even if reasonably reliable background rates can be produced, challenges for their effective utilization cannot all be tackled today in Belgium, as summarized in Table 4. Two important challenges are the current under-reporting of adverse events to the competent authority and the relatively small population size of vaccine recipients in Belgium. The latter challenge cannot be solved and points to the need of vaccine safety surveillance at the European level. Such European surveillance is developing rapidly.

Given these elements, it doesn't seem appropriate to invest in the development of a background rate approach for vaccine safety surveillance in Belgium. This certainly does not mean that vaccine safety surveillance is in a deadlock. Improving the reporting of AEFIs to FAMHP is essential. The direct declaration of AEFIs by consumers, which will be implemented in the short term, could be a great step forward in that direction. Better reporting practices by healthcare providers and a more standardized classification of AEFIs are also important targets. Rapid analysis and interpretation of potential safety signals sent back by EMA or other sources is crucial for appropriate risk communication and risk minimization.

The possibility of implementing alternative strategies of vaccine safety surveillance in Belgium was beyond the scope of this project. Such strategies should be based on an overall assessment of the health information needs in Belgium and come up with a global data collection and analysis plan. However, it should be noted that data mining is already done by EMA on EudraVigilance, a dataset including safety reports to

FAMHP. Also, cohort studies and self-controlled case series could be possibly implemented through the utilization of the IMA dataset which contains information both on certain types of vaccination and on the occurrence of hospitalization, death, and the utilization of specific health services or medicines. The feasibility of such an approach should be further assessed.



■ APPENDICES

APPENDIX 1. COMPUTATION OF OBSERVED TO EXPECTED RATIO

In case the number of observed events (O) is small, the Poisson distribution is skewed and the normal approximation not anymore valid. In such case, Byar suggested an accurate approximation to the exact Poisson test:

$$x = \sqrt[2]{9\tilde{O}} * \left(1 - \frac{1}{9\tilde{O}} - \sqrt[3]{\frac{E}{\tilde{O}}}\right)$$

where $\tilde{O} = O$ if O exceeds E , and $\tilde{O}=O+1$ otherwise, and referring it to tables of the unit normal distribution.¹³

Confidence intervals around OE can be computed, μ_L and μ_U being respectively the lower and upper limits for the mean $\mu=E(D)$ of the Poisson distributed observation D.

$$\mu_L=O*(1-1/9O-Z_{\alpha/2}/3O^{1/2})^3$$

$$\mu_U=(O+1)*[1-1/(9(O+1))+Z_{\alpha/2}/(3(O+1))]^{1/2}]^3$$

where $Z_{\alpha/2}$ = value of the unit normal distribution for a given significance level (alpha).

The OE_L can be calculated as:

$$OE_L=\mu_L/E$$

$$OE_U=\mu_U/E.$$

For computing 95% confidence intervals, the values presented in Table 25 can be used as follows:

$$OE_L=OE * L$$

$$OE_U= OE * U$$



Table 25 – Values of 95% confidence limit factors for estimating a Poisson-distributed variable¹³

Observed number on which estimate is based (n)	Lower limit factor (L)	Upper limit factor (U)	Observed number on which estimate is based (n)	Lower limit factor (L)	Upper limit factor (U)	Observed number on which estimate is based (n)	Lower limit factor (L)	Upper limit factor (U)
1	0.0253	5.57	21	0.619	1.53	120	0.833	1.200
2	0.121	3.61	22	0.627	1.51	140	0.844	1.184
3	0.206	2.92	23	0.634	1.50	160	0.854	1.171
4	0.272	2.56	24	0.641	1.48	180	0.862	1.160
5	0.324	2.33	25	0.647	1.48	200	0.868	1.151
6	0.367	2.18	26	0.653	1.47	250	0.882	1.134
7	0.401	2.06	27	0.659	1.46	300	0.892	1.121
8	0.431	1.97	28	0.665	1.45	350	0.899	1.112
9	0.458	1.90	29	0.670	1.44	400	0.906	1.104
10	0.480	1.84	30	0.675	1.43	450	0.911	1.098
11	0.499	1.79	35	0.697	1.39	500	0.915	1.093
12	0.517	1.75	40	0.714	1.36	600	0.922	1.084
13	0.532	1.71	45	0.729	1.34	700	0.928	1.078
14	0.546	1.68	50	0.742	1.32	800	0.932	1.072
15	0.560	1.65	60	0.770	1.30	900	0.936	1.068
16	0.572	1.62	70	0.785	1.27	1 000	0.939	1.064
17	0.583	1.60	80	0.798	1.25			
18	0.593	1.58	90	0.809	1.24			
19	0.602	1.56	100	0.818	1.22			
20	0.611	1.54						

APPENDIX 2. BELGIAN DATABASES FOR COMPUTING BACKGROUND RATES

Appendix 2.1. Minimal Clinical Data

Data providers

The registration is mandatory for every hospital in Belgium since October 1990 all for each admission through a standard form containing a defined set of clinical data including ICD-coded diagnoses and procedures. These discharge abstracts are termed Minimal Clinical Data (MCD) and contain patient data (among which year of birth, gender, residence, and anonymous hospital and patient identifiers), stay data (among which year and month of admission and discharge, length of stay, transfer to another hospital with specification of the type of hospital) and an unlimited number of diagnoses and procedures. At the moment of discharge from the hospital all hospitalisations are registered for which:

- At least one day of hospitalisation was billed
- A forfait was billed when the patient leaves the hospital on the same day he was hospitalised
- If he was taken in by the emergency department without having been billed under 1 and 2
- All newborn without any billing

The objective of the MCD as stated by the federal government is (source: website federal government):

- Assess the need for hospital services
- Determine their qualitative and quantitative criteria for recognition and services
- Organise the finances of the hospitals
- Determine the policy concerning the practice of medicine
- Determine an epidemiological policy



Access to data

KCE has in principle direct access to data on condition that these are sufficiently aggregated to ensure anonymity of individual patients.

Case definition (signs, symptoms, inpatient or outpatient, any tests)

ICD-9-CM encoding is used

Population covered and denominators (including age groups)

All persons covered by the Belgian compulsory insurance so denominators can be taken from the Belgian census data.

Representativeness of the source population

Apart for groups that are not covered by health insurance, source population is comprehensive. For surveillance purposes only cases that end up in the inpatient care are included, so representativeness is disease specific and variable.

Sensitivity (or ascertainment) of the data source and other factors potentially influencing the probability of event capture and rate calculation (ex. financial incentives, specific tests required)

There is no confirmation of the diagnoses, sensitivity of the number of cases depends on:

- The chance that a patient ends up in a hospital, this may be problematic for milder diseases.
- The way the diseases are declared, the MCD is in the first place a database used for reimbursement purposes, hospitals may optimise their revenue. This is mainly due to the use Diagnosis Related Groups (DRGs) as a measure of case mix, linking a particular DRG to the length of stay (LOS), and determining in this way the total cost and the amount that a hospital is reimbursed. This leads to a phenomenon described as "DRG creep", the systematically and deliberately overvaluing of the case mix. This was illustrated for Belgium by a study of Aelvoet et al.,¹ where amongst others thrombocytopenia, a condition that is a vaccine related adverse effect, was shown to be (mis)used for this purpose.

Timeliness (lag between disease onset and disease report, and lag between report and data access)

The Hospital Clinical Records (HCR) records are afterwards linked to the Hospital Billing Records (HBR), yearly transmitted by the national health insurance companies (HIC) to the National Institute for Health and Disability Insurance (NIHDI) and assembling all NIHDI remunerations for each hospital stay. HCR-HBR linkage is performed by a legally instituted 'Technical Cell' and requires separately sent matching tables containing for each identifiable hospital stay an unique patient pseudonym created by two separately executed hashings: the first by the hospital or HIC respectively and the second by an appointed security advisor of the MOH. Linkage process takes about 2 years to completion and full validation. Linkage percentages increased over the years and exceed nowadays 95% overall.

Variables available (age, sex, specific subgroups)

For each hospitalized patient, information such as date of birth, sex, postal code of domicile and other information such as length of hospital stay (LOS), hospital ward and bed type occupation etc., is recorded,

Geographical information needs to be aggregated at a sufficiently high level in order to maintain confidentiality.

Conclusion: Potentially useful for a number of diseases, especially if the patient has a very high chance of ending up in an inpatient department in the course of the disease. However it should be independently validated.



Appendix 2.2. Carenet

Data providers

Carenet is a secure internet platform allowing the exchange of information between hospitals and health insurance companies about individual hospitalizations: time of admission, stay duration, diagnosis and medical procedures which reimbursement is allowed by INAMI/RIZIV. The main purpose of Carenet is simplifying and accelerating such data transfer. Carenet might thus present the advantage of giving access to data on specific health conditions more rapidly than MCD. However, it is worth mentioning that the diagnosis field is alphanumerical, i.e. either free text or ICD-9-CM codes can be used.

Access to data

In principle data are for internal use only, but for scientific purposes data can be accessed through following procedures involving the steering committee of the intermutualistic agency and the '7 club'. Two projects were done: intussusceptions for rotavirus, where a case control study was set up. The Federal agency for drugs approval (FAMHP) introduced a demand for data on Guillain-barré.

Procedures are rather lengthy for the moment but may become shorter in the future.

Case definition (signs, symptoms, inpatient or outpatient, any tests)

Diagnosis are encoded in free text, so text mining techniques are needed to analyse the date.

Sometimes hospitals use ICD-9-CM encoding or DSM4 for psychiatric conditions, but this is also done in free text.

Population covered and denominators (including age groups)

The system is compulsory for all hospitals apart 15 smaller health structures mainly involved in revalidation so all cases that come in contact with an inpatient facility should be covered.

Representativeness of the source population

Apart for groups that are not covered by health insurance source population is comprehensive.

Sensitivity (or ascertainment) of the data source and other factors potentially influencing the probability of event capture and rate calculation (ex. financial incentives, specific tests required) The interview of key informants revealed that the data validity is likely to be extremely variable among hospitals. Some hospitals enter the same ICD-9-CM coded data that they deliver to the MCD database, and this task is performed by professional coders. In other hospitals, this field is filled in by undetermined clinical staff essentially in the form of free text. In this latter case, text mining techniques are needed to extract and analyze the data. Moreover, it is worth mentioning that the only legal obligation is to fill in the diagnosis field, not to fill it with accurate and comprehensive data, and that there is no quality control on the diagnosis. Carenet also shares with MCD the limitation of being currently limited to inpatient data.

Timeliness (lag between disease onset and disease report, and lag between report and data access)

Reporting delay is a month, but it is not clear how fast data can be accessed, probably depends on perceived urgency and political will. The need for test mining slows down the speed at which data are available, introduction of ICD-9 codes could speed things up.

Variables available (age, sex, specific subgroups)

National number is recorded ("rijksregisternummer/numéro de register national") so database can be linked to other sources.

Conclusion: Can be used for background rates for adverse effects that require hospitalization, probably available faster than the Hospital Clinical Records database.

Appendix 2.3. Special Solidarity Fund (Bijzonder solidariteitsfonds/Fonds spécial de solidarité)

Following descriptions come from kce report 133: Optimalisatie van de werkingsprocessen van het Bijzonder Solidariteitsfonds.¹²⁰

Data providers

The Special Solidarity Fund (SSF) reimburses costs of medical treatments that are not covered by the compulsory health care insurance system (or any other insurance) and that are related to rare indications, rare diseases, innovative treatment techniques, chronically ill children and medical treatment abroad. To be eligible for reimbursement by the SSF, the medical treatment has to be expensive, threatening the vital functions of the patient, have a proven scientific value and effectiveness and be prescribed by a specialized medical doctor. There may be no alternative that is reimbursed by the compulsory health care insurance system and the patient may not have other rights for reimbursement from other private or public insurance systems. The budget of the SSF varies substantially over the years. Expenses are often determined by changes that occur in the reimbursement of medical costs in the compulsory health care insurance system.

Access to data

KCE has access.

Case definition (signs, symptoms, inpatient or outpatient, any tests)

ICD-9-CMⁿ encoding is used.

Population covered and denominators (including age groups)

All persons covered by the Belgian compulsory insurance so denominators can be taken from the Belgian census data.

Representativeness of the source population

Apart for groups that are not covered by health insurance, source population is comprehensive. For surveillance purposes only cases that apply for special reimbursement are included.

ⁿ International classification of diseases, version 9, clinical modification (WHO)

Sensitivity (or ascertainment) of the data source and other factors potentially influencing the probability of event capture and rate calculation (ex. financial incentives, specific tests required)

Applications for reimbursement of medical costs by the SSF start from an individual request introduced by the patient at the local sickness fund level that transfer them to the national sickness funds. From there the application passes to the SSF. Applications are examined from an administrative point of view (check if all required documents are present) and a medical point of view (check if the application meets the medical criteria for reimbursement by the SSF). Decisions on SSF applications are taken by the College of medical directors. For certain types of applications the decision can be delegated to one member of the college or to the local sickness funds. Appeals are handled by the labor courts.

Usefulness for calculations of background rates or signal detection.

Although part of the diseases are rare diseases that may be eligible for funding, it will be difficult to obtain valid data, mainly for following reasons:

- Interviews with different stakeholders indicate that the fund is not well known and that this is perceived to be a problem. This is reflected in the fact that applications come from a limited number of centers.
- Decision criteria are vague and it is not clear, it is a fund of last resort that you can use if all other channels of reimbursement are exhausted, this uncertainty makes that not everybody will choose to apply.
- Reimbursement evolves and depends on the evolution in the criteria of other reimbursement channels, be it the regular compulsory health care insurance system (or any other insurance) or the orphan drug fund. This evolves in time.

These elements make that it is unclear what fraction of eligible patients would end up in the database, moreover, this fraction is likely to vary over time.

Timeliness (lag between disease onset and disease report, and lag between report and data access)

Reporting at regular interval, although this has been recommended by the KCE in their evaluation report.

Variables available (age, sex, specific subgroups)



Conclusion: These elements limit strongly the usefulness of the data, for signal detection and for calculation of background rates.

Appendix 2.4. Integoo

Data providers

The Intego network is the first computerized network of voluntary sentinel general practitioners in Flanders, the northern Dutch speaking part of Belgium. The network is organised within the department of General Practice of the Katholieke Universiteit Leuven and provides data on incidences and prevalence of all diseases in Flanders, but also on laboratory tests and drug prescriptions from 1994 onward. Since spring 2009 the registration network includes 55 GP practices. These are spread across Flanders. Every year only two to three practices leave the network and are replaced by new practices. In these 55 practices are currently 92 GPs active, 67 (73%) men and 25 (27%) women. This represents 1.05% of all GPs working in Flanders. Sixteen work as a duo or group practice and 39 as solo physician.

Access to data

Incidence rates are available on a website per ICPC2 code per year per age-group. For more detailed information Intego should be contacted

Case definition (signs, symptoms, inpatient or outpatient, any tests)

ICPC encoding is used, for most common adverse event following immunization (AEFI) this encoding lacks specificity

Population covered and denominators (including age groups)

Currently there are data from 215 251 different patients included in the database. In 2008 there were 90 324 different patients seen in 55 general practices, this is the yearly contact group (YCG). To know the entire practice population (PP), we must also take into account the patients who did not contact the practice in the corresponding year. Therefore we take the percentage of the population that contacts a GP, which is known by the Inter Mutualistic Agency. By dividing the YCG by this percentage, we obtain an estimated practice population. Calculated in this way, the

practice population of the Intego database is currently 1.95% of the Flemish population.

Representativeness of the source population

The patient population in the Intego database is representative of the Flemish population on age, sex and average income. The proportion of both populations divided in standard age groups shows only minor differences (Figure 1). This also applies if the proportions are broken down by sex.

Sensitivity (or ascertainment) of the data source and other factors potentially influencing the probability of event capture and rate calculation (ex. financial incentives, specific tests required)

Specificity depends on the way data are entered, no verification is done. Only patients that contact a GP come into the database.

Timeliness (lag between disease onset and disease report, and lag between report and data access)

Data for 2010 are now on the website.

Variables available (age, sex, specific subgroups)

Age group (10 year and under five), sex, year of diagnosis.

Conclusion: Sample size is small for diseases with an incidence between 1 and 50 per 100 000. Moreover, the real target population is only indirectly measured.

Appendix 2.5. IPH Sentinel Practice (« peilpraktijken/réseau sentinelle »)

Consist of a network of around 200 GPs, that register a number of interventions or diseases. What is registered changes every year, until now no items were registered that could be useful for our purposes.

° <http://www.intego.be>



Appendix 2.6. Vaccinnet

Data providers

Vaccinnet was established as an online ordering system for all vaccines made available for the vaccination program in Flanders. This vaccine ordering system is linked to a vaccination database. Follow-up of each vaccinator's vaccine stockpile facilitates vaccine ordering when a critical threshold is reached. As an intrinsic condition all Vaccinnet users have to register recent vaccination data in a population-linked database. This vaccination database is made available to all users of Vaccinnet.

Representativeness of the source population

By October 1st 2010 about 57% of GPs and 50% of paediatricians made use of Vaccinnet. Considering that all recent vaccinations of well baby clinics and schoolmedicine are documented in the system, the vaccination database of Vaccinnet accounts for more than 90% of all recently given vaccinations.

Access to data

Access should be

Sensitivity (or ascertainment) of the data source and other factors potentially influencing the probability of event capture and rate calculation (ex. financial incentives, specific tests required)

Not applicable, is only useful for data on vaccination.

Timeliness (lag between disease onset and disease report, and lag between report and data access)

Data are in principle available in real time, procedures for permissions to use them may be elaborated.

Variables available (age, sex, specific subgroups)

Age, sex and data on vaccination status.

Conclusion: Vaccination can be identified with 'national registry number (rijkregisternummer/numéro de register national), if a linkage is possible this could give opportunities. A feasibility study on a possible link with the electronic medical files of the clinician is ongoing

Background rates

Appendix 2.7. Pedisurv

Data providers

In 2002 the network PediSurv (**Pediatric diseases Surveillance**) was developed in order to collect information about some vaccine preventable diseases according to European Decision (2119/98/CE). Mumps, measles, rubella, acute flaccid paralysis (AFP) and invasive pneumococcal diseases (IPD) in 2007 were included since they were not registered by other networks or under mandatory notifications. All Belgian paediatricians and GP working in Brussels were invited to participate to this network. Participation is voluntary and requests a monthly reporting of the diseases even in case of a zero case notification. Since data entry from paper form induced mistakes, a web application was developed also to reduce this time consuming activity. Participants can directly enter the data.

Access to data

Not readily available.

Case definition (signs, symptoms, inpatient or outpatient, any tests)

ICPC encoding is used, for most common AEFI this encoding lacks specificity.

Population covered and denominators (including age groups)

Unclear, around 65% of pediatricians would participate.

Representativeness of the source population

Unclear.

Sensitivity (or ascertainment) of the data source and other factors potentially influencing the probability of event capture and rate calculation (ex. financial incentives, specific tests required)

Main focus on vaccine preventable diseases among children that contact a paediatrician. An indication is the reporting rate of flaccid paralysis, that is estimated at 1/100 000 amongst children under 15, which for Belgium would imply 18 cases. In 2010 only 4 cases (22%) were declared, indicating important underreporting.

Timeliness (lag between disease onset and disease report, and lag between report and data access)



Data for 2010 are now on the website.

Variables available (age, sex, specific subgroups)

Age-group (10 year and under five), sex, year of diagnosis.

Conclusion: Is a surveillance tool mainly for vaccine preventable diseases and as such not really useful for our surveillance of vaccine safety.

Appendix 2.8. Sentinel laboratories

A network of 101 sentinel microbiology laboratories with voluntary unpaid participation representing 58% of all in 2010 recognized private or hospital microbiology laboratories situated in 33 of 43 Belgian districts; no potential AEFI are monitored, so this database is not really useful for our purposes. The same is true for a number of other disease monitoring initiatives:

- Influenza
- AIDS reference laboratoria
- Creutzfeldt-Jakob Disease (CJD)
- Sexually transmitted infection

Appendix 2.9. Kinderdatabank system IKAROS

IKAROS stands for GelIntegreerd Kind Activiteiten Regio OndersteuningsSysteem.

Data providers

IKAROS is a database meant to be a support for the functioning of the preventive family support, at the operational, tactical and policy level. Data are collected on all children in Flanders from birth. Files on the children are closed if during 15 months a staff member of the regional teams of Kind en Gezin did not have at least one contact with the concerned family. Registration is continuous.

Access to data

Anonymised data can be accessed for scientific purposes after application.

Case definition (signs, symptoms, inpatient or outpatient, any tests)

Only limited information on diagnosis available.

Population covered and denominators (including age groups)

All children that come into contact with Kind en Gezin are in the database.

Representativeness of the source population

Nearly all children are included.

Sensitivity (or ascertainment) of the data source and other factors potentially influencing the probability of event capture and rate calculation (ex. financial incentives, specific tests required)

Only limited information on diagnosis, except sudden infant death and anaphylactic reactions.

Timeliness (lag between disease onset and disease report, and lag between report and data access)

Registration is continuous but it is unclear how fast data can be accessed if it were needed for the evaluation of an adverse effect. Yearly reports are published on the state of the children in Flanders. This report contains information on the incidence of Sudden infant death in Flanders.

Variables available (age, sex, specific subgroups)

Age, sex, birthplace, contains also information on educational level and socioeconomic status. Contains information on vaccination status, date of vaccination and occurrence of anaphylactic reactions, gets information from the Vaccinnet database, a database used for distribution of vaccines in Flanders.

Conclusion: Can be used for estimation of background rates of sudden infant death in Flanders, these statistics are already published. If linkage is possible the data on vaccination could be used as well.



Appendix 2.10. Banque de données Médico-Sociales de l'ONE (Office de la naissance et de l'enfance)

Is the counterpart of IKAROS in the French speaking part of Belgium.

Data providers

Database meant to be a support for the functioning of the preventive family support, at the operational, tactical and policy level. Data are collected on all children in the French speaking part of Belgium from birth, data are collected until 30 months.

Access to data

Yearly reports are published, last report is from 2007. Anonymised data can be accessed for scientific purposes after application.

Case definition (signs, symptoms, inpatient or outpatient, any tests)

Limited information on diagnosis.

Population covered and denominators (including age groups)

All children that come into contact with ONE are in the database.

Representativeness of the source population

Data collected on a non representative sample.

Sensitivity (or ascertainment) of the data source and other factors potentially influencing the probability of event capture and rate calculation (ex. financial incentives, specific tests required).

Only limited information on diagnosis, except sudden infant death.

Timeliness (lag between disease onset and disease report, and lag between report and data access)

Registration is continuous but it is unclear how fast data can be accessed if it were needed for the evaluation of an adverse effect. Yearly reports are published last report is from 2007. This report contains information on the incidence of Sudden infant death.

Variables available (age, sex, specific subgroups)

Age, sex, birthplace, contains also information on educational level and socioeconomic status. Contains information on vaccination status, date of vaccination and occurrence of anaphylactic reactions, gets information

from the Vaccinnet database, a database used for distribution of vaccines in Flanders

Conclusion: Can be used for estimation of background rates of sudden infant death, these statistics are already published. If linkage is possible the data on vaccination could be used as well.

Appendix 2.11. Database do the SPE (Studycentre for Perinatal Epidemiology)

Collects data from all obstetric centres en Flanders on perinatal mortality, morbidity of mother and child. Can be accessed after a written request to the scientific board that comes together 6 times a year.

Appendix 2.12. Mortality monitoring (MOMO)

Was set up to monitor excess mortality during health waves.



APPENDIX 3. SEARCH TERMS FOR LITERATURE REVIEW

Appendix 3.1. Sudden infant deaths

Search terms in Medline(Pubmed): ((("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "epidemiology"[MeSH Terms]) AND (sudden infant death[All Fields] OR sudden infant death/blood[All Fields] OR sudden infant death/classification[All Fields] OR sudden infant death/complications[All Fields] OR sudden infant death/diagnosis[All Fields] OR sudden infant death/embryology[All Fields] OR sudden infant death/enzymology[All Fields] OR sudden infant death/epidemiology[All Fields] OR sudden infant death/ethnology[All Fields] OR sudden infant death/etiology[All Fields] OR sudden infant death/genetics[All Fields] OR sudden infant death/history[All Fields] OR sudden infant death/immunology[All Fields] OR sudden infant death/metabolism[All Fields] OR sudden infant death/microbiology[All Fields] OR sudden infant death/mortality[All Fields] OR sudden infant death/nursing[All Fields] OR sudden infant death/pathology[All Fields] OR sudden infant death/physiopathology[All Fields] OR sudden infant death/radiography[All Fields] OR sudden infant death/therapy[All Fields] OR sudden infant deaths[All Fields])) AND ("humans"[MeSH Terms] AND (English[lang] OR French[lang] OR Spanish[lang]) AND "infant"[MeSH Terms] AND ("2000/01/01"[PDAT] : "2012/04/01"[PDAT])))

Appendix 3.2. Sudden deaths (≥ 1 year)

("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "epidemiology"[MeSH Terms]) AND ("death, sudden"[MeSH Terms] OR ("death"[All Fields] AND "sudden"[All Fields]) OR "sudden death"[All Fields] OR ("sudden"[All Fields] AND "death"[All Fields])) AND ("humans"[MeSH Terms] AND ("2000/01/01"[PDAT] : "2012/04/01"[PDAT]))

Appendix 3.3. Guillain-Barré disease

Search terms in Medline(Pubmed): ""Guillain-Barre Syndrome"[All Fields] AND ((("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "incidence"[All Fields] OR "incidence"[MeSH Terms])) AND ("2000/01/01"[PDAT] : "2012/04/01"[PDAT])).

APPENDIX 4. “NON-SPECIFIC” REIMBURSEMENT REQUEST FORM FOR IMMUNOGLOBULIN’S FROM ATC CODE J06BA01

Modèle de formulaire de demande de remboursement « non-spécifique » (*) visé à l'article 80, alinéa 10

(*) Formulaire de demande de remboursement utilisable pour introduire une demande de remboursement pour une spécialité dont les conditions de remboursement fixées au chapitre IV n'imposent pas un formulaire de demande spécifique, pour autant que l'autorisation de remboursement prévue soit un document dont le modèle est arrêté sous « b » ou « d » de l'annexe III de la liste.

I – Identification du bénéficiaire (nom, prénom, N°-NISS) :

II – Eléments à attester par le médecin traitant :

Je soussigné, docteur en médecine, certifie que le patient mentionné ci-dessus remplit toutes les conditions nécessaires pour obtenir le remboursement de la spécialité

_____ (nom de la spécialité demandée)

telles que ces conditions figurent au § _____ (**) du chapitre IV de l'A.R. du 21 décembre 2001 :

_ Il s'agit d'une première période d'autorisation;

_ Il s'agit d'une période de prolongation d'autorisation.

Je m'engage à tenir à la disposition du médecin-conseil les éléments de preuve établissant que le patient concerné se trouve dans la situation attestée, y compris, le cas échéant, lorsque les conditions prévoient que la demande doit être rédigée par un médecin titulaire d'une qualification médicale particulière, une attestation d'un médecin possédant cette qualification, qui confirme que les conditions sont bien remplies chez le patient concerné.

Sur base de tous ces éléments, j'atteste que ce patient nécessite de recevoir le remboursement de cette spécialité pour la période prévue dans la réglementation du paragraphe mentionné ci-dessus.

III – Identification du médecin traitant (nom, prénom, adresse, N°INAMI) :

_____ (nom)

_____ (prénom)

1- _____ - _____ - _____ (N° INAMI)

____ / ____ / ____ (DATE)

(CACHET) (SIGNATURE DU MEDECIN)

(*) Le présent formulaire de demande de remboursement n'est utilisable que pour introduire une demande de remboursement pour une spécialité dont les conditions de remboursement fixées au chapitre IV n'imposent pas un formulaire de demande spécifique, et pour autant que l'autorisation de remboursement prévue soit un document dont le modèle est arrêté sous « b » ou « d » de l'annexe III de la liste.

(**) Le texte du paragraphe concerné peut être joint en annexe avec le présent formulaire.



APPENDIX 5. REIMBURSEMENT CRITERIA OF IMMUNOGLOBULIN'S FOR EXTRAVASCULAR ADMINISTRATION (J06BA01)

Chapter IV	§ 3 410 000
Immunoglobulins: De specialiteit is vergoedbaar indien aangetoond wordt dat ze voor één van de volgende indicaties werd aangewend: 1. Primaire immuundeficiëntiesyndromen: 1) aangeboren of verworven agammaglobulinemie of hypogammaglobulinemie waarbij, ofwel het totale IgG gehalte ofwel het IgG ₂ - ofwel het IgG ₃ -gehalte, als volgt verlaagd zijn: - volwassenen: IgG gehalte < 7,50 g/l; IgG ₂ -gehalte < 1,50 g/l; IgG ₃ -gehalte < 0,20 g/l; - kinderen: onder de norm van het laboratorium, rekening houdend met een aan de leeftijd gekoppelde controlepopulatie. Die hypogammaglobulinemie moet tot gevolg hebben gehad dat er ernstige recidiverende infecties zijn opgetreden of chronische bacteriële infecties die gedocumenteerd zijn en waarvoor herhaaldelijk, gepaste en gerichte antibioticatherapie noodzakelijk was. De vergoeding wordt geweigerd als de IgG/IgG ₂ /IgG ₃ -deficiëntie te wijten is aan een chronische behandeling met corticosteroïden bijvoorbeeld bij chronisch obstructief longlijden of het gevolg is van verlies via de darm of de urine. 2) congenitale antipolysaccharide antistofdeficiëntie die tot gevolg heeft dat recidiverende infecties zijn opgetreden waarvoor herhaaldelijk antibioticatherapie noodzakelijk was. Deze deficiëntie moet gedocumenteerd zijn door het falen van de anti-lichaam-productie na pneumococcenvaccinatie. 2. Myeloom en CLL met ernstige secundaire hypogammablobulinemie en recidiverende infecties. Op grond van een omstandig verslag dat is opgemaakt door een geneesheerspecialist verantwoordelijk voor de behandeling, reikt de adviserend genees-heer aan de rechthebbende de machtiging uit waarvan het model is vastgesteld onder "b" van de bijlage III van het koninklijk besluit van	Gammanorm, Hizentra, Subcuvia, Vivaglobin La spécialité est remboursable s'il est démontré qu'elle a été utilisée dans une des situations suivantes: 1. Syndromes d'immunodéficience primaires: 1) agammaglobulinémie ou hypogammaglobulinémie congénitale ou acquise dont soit la teneur totale en IgG, soit la teneur en IgG2 ou IgG3 est la suivante: - adultes : taux d'IgG < 7,50 g/l ; taux d'IgG2 < 1,50 g/l ; taux d'IgG3 < 0,20 g/l ; - enfants : valeur inférieure à la norme du laboratoire en tenant compte d'une population de contrôle appariée à l'âge. Cette hypogammaglobulinémie doit avoir eu pour conséquence la survenue d'infections récurrentes graves ou d'infections bactériennes chroniques, documentées et qui ont nécessité une antibiothérapie répétée et ciblée appropriée. Le remboursement est refusé si la déficience en IgG/IgG2/IgG3 est due à un traitement chronique avec des corticostéroïdes par exemple comme dans la bronchopneumopathie chronique obstructive ou est le résultat d'une perte intestinale ou par les urines. 2) déficience congénitale en anticorps antipolysaccharides qui a comme conséquence que des infections récidivantes sont apparues pour lesquelles une antibiothérapie était nécessaire. Cette déficience doit être documentée par l'échec de la production d'anticorps après vaccination par les pneumocoques. 2. Myélome et CLL avec hypogammaglobulinémie secondaire sévère et infections récidivantes. Sur base d'un rapport circonstancié établi par un médecin spécialiste responsable du traitement, le médecin conseil délivre au bénéficiaire l'autorisation dont le modèle est fixé sous "b" de l'annexe III de l'arrêté royal



21.12.2001 en waarvan de geldigheidsduur beperkt is tot 12 maanden.

De gelijktijdige terugbetaling van de specialiteit met andere specialiteiten op basis van immunoglobulinen (vergoedingsgroepen A-21 en A-78) wordt nooit toegestaan.

Voor de eerste aanvraag tot tegemoetkoming en desgevallend voor de aanvraag tot verlenging van de machtiging kan vrijblijvend gebruik gemaakt worden van het volgende formulier : "Niet specifiek" aanvraagformulier (niet verplicht)

du 21.12.2001 et dont la durée de validité est limitée à 12 mois.

Le remboursement simultané de la spécialité avec des spécialités à base d'immunoglobulines (groupes de remboursement A-21 et A-78) n'est jamais autorisé.

La première demande de remboursement et le cas échéant la demande de prolongation de l'autorisation peut être faite librement au moyen du formulaire suivant : Formulaire de demande "non-spécifique" (non obligatoire)



APPENDIX 6. REIMBURSEMENT CRITERIA OF IMMUNOGLOBULIN'S FOR INTRAVASCULAR ADMINISTRATION (J06BA02)

Chapter IV	§ 90 000
Immunoglobulins: De specialiteit is vergoedbaar indien aangetoond wordt dat ze voor één van de volgende indicaties werd aangewend: 1. Primaire immuundeficiëntiesyndromen: 1) aangeboren of verworven agammaglobulinemie of hypogammaglobulinemie waarbij, ofwel het totale IgG gehalte ofwel het IgG2- ofwel het IgG3 gehalte, als volgt verlaagd zijn: <ul style="list-style-type: none">- volwassenen: IgG gehalte < 7,50 g/l; IgG2 gehalte < 1,50 g/l; IgG3 gehalte < 0,20 g/l;- kinderen: onder de norm van het laboratorium, rekening houdend met een aan de leeftijd gekoppelde controlepopulatie. <p>Die hypogammaglobulinemie moet tot gevolg hebben gehad dat er ernstige recidiverende infecties zijn opgetreden of chronische bacteriële infecties die gedocumenteerd zijn en waarvoor herhaaldelijk, gepaste en gerichte antibioticatherapie noodzakelijk was. De vergoeding wordt geweigerd als de IgG/IgG2/IgG3-deficiëntie te wijten is aan een chronische behandeling met corticosteroïden bijvoorbeeld bij chronisch obstructief longlijden of het gevolg is van verlies via de darm of de urine.</p> <p>2) congenitale antipolysaccharide antistofdeficiëntie die tot gevolg heeft dat recidive-ren-de infecties zijn opge-treden waarvoor her-haaldelijk antibiotica-thera-pie noodza-kelijk was. Deze deficiëntie moet gedocu-men-teerd zijn door het falen van de anti-lichaam-productie na pneumococcenvaccinatie.</p> <p>2. Myeloom en CLL met ernstige secundaire hypogammablobulinemie en recidiven-de infec-ties.</p> <p>De gelijktijdige terugbetaling van de specialiteit met andere specialiteiten op basis van immunoglobulinen (vergoedingsgroepen A-21 en A-78) wordt nooit toegestaan.</p>	Gammagard La spécialité est remboursable s'il est démontré qu'elle a été utilisée dans une des situations suivantes: 1. Syndromes d'immunodéficience primaires: 1) agammaglobulinémie ou hypogammaglobulinémie congénitale ou acquise dont soit la teneur totale en IgG, soit la teneur en IgG ₂ ou IgG ₃ est la suivante: - adultes : taux d'IgG < 7,50 g/l ; taux d'IgG ₂ < 1,50 g/l ; taux d'IgG ₃ < 0,20 g/l; - enfants : valeur inférieure à la norme du laboratoire en tenant compte d'une population de contrôle appariée à l'âge. Cette hypogammaglobulinémie doit avoir eu pour conséquence la survenue d'infections récurrentes graves ou d'infections bactériennes chroniques, documentées et qui ont nécessité une antibiothérapie répétée et ciblée appropriée. Le remboursement est refusé si la déficience en IgG/IgG ₂ -/IgG ₃ est due à un traitement chronique avec des corticostéroïdes par exemple comme dans la bronchopneumopathie chronique obstructive ou est le résultat d'une perte intestinale ou par les urines. 2) déficience congénitale en anticorps antipolysaccharides qui a comme conséquence que des infections récidivantes sont apparues pour lesquelles une antibiothérapie était nécessaire. Cette déficience doit être documentée par l'échec de la production d'anticorps après vaccination par les pneumocoques. 2. Myélome et CLL avec hypogammaglobulinémie secondaire sévère et infections récidivantes. Le remboursement simultané de la spécialité avec des spécialités à base d'immunoglobulines (groupes de remboursement A-21 et A-78) n'est jamais autorisé. 3. Traitement d'enfants n'ayant pas dépassé l'âge de 18 ans et atteints de SIDA.

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3. Ter behandeling van kinderen die niet ouder zijn dan 18 jaar en lijden aan AIDS.
4. Idiopathische trombocytopenische purpura:
- bij kinderen;
 - bij volwassenen met een hoog risico op bloedingen of die wachten op een nakende heelkundige ingreep;
5. Syndroom van Guillain-Barré bij patiënten met één van de volgende symptomen:
- progressieve parese (de patiënt kan niet meer dan 10 meter onafhankelijk lopen);
 - aanwijzingen van een respiratoire aandoening (klinische observatie of aangetoond door meting van de vitale capaciteit aan het bed van de patiënt);
 - tekens van bucco-faryngeale parese.
6. Ziekte van Kawasaki.
7. Preventie van infecties bij patiënten die een allogene beenmergtransplantatie ondergaan.
8. Ter behandeling van sepsis optredend bij prematuren en in de neonatale periode.
- De gelijktijdige terugbetaling van de specialiteit met andere specialiteiten op basis van immunoglobulinen (vergoedingsgroepen A-21 en A-78) wordt nooit toegestaan.
- De voorschrijvende geneesheer-specialist verantwoordelijk voor de behande-ling moet de bewijsstukken waaruit blijkt dat aan alle voornoemde voorwaarden wordt voldaan, desgevraagd kunnen bezorgen aan de adviserend geneesheer van de verzekeringsinstelling.
4. Purpura thrombocytopénique idiopathique:
- chez des enfants;
 - chez des adultes qui présentent un grand risque d'hémorragies ou chez ceux qui sont en attente d'une intervention chirurgicale imminente;
5. Syndrome de Guillain-Barré chez les patients qui présentent un des symptômes suivants:
- parésie progressive (le patient ne peut marcher plus de 10 mètres indépendamment);
 - signes d'une atteinte respiratoire (observée cliniquement ou démontrée par la capacité vitale au lit du patient);
 - signes de parésie bucco-pharyngée.
6. Maladie de Kawasaki.
7. Prévention des infections chez des patients subissant une transplantation allogène de moelle osseuse.
8. Traitement de septicémie chez des prématurés et pendant la période néonatale.
- Le remboursement simultané de la spécialité avec des spécialités à base d'immunoglobulines (groupes de remboursement A-21 et A-78) n'est jamais autorisé.
- Le médecin prescripteur spécialiste, responsable du traitement, doit pouvoir fournir au médecin-conseil de l'organisme assureur, à la demande de celui-ci, les pièces justificatives qui montrent que toutes les conditions ci-dessus sont remplies.
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**Chapter IV****§ 3 190 000****Immunoglobulins:**

De specialiteit is vergoedbaar indien aangetoond wordt dat ze voor één van de volgende indicaties werd aangewend:

1. Primaire immuundeficiëntiesyndromen:

1) aangeboren of verworven agammaglobuline-mie of hypogammaglobulinemie waarbij, ofwel het totale IgG gehalte ofwel het IgG₂- ofwel het IgG₃-gehalte, als volgt verlaagd zijn:

- volwassenen: IgG gehalte < 7,50 g/l; IgG₂-gehalte < 1,50 g/l; IgG₃-gehalte < 0,20 g/l.

- kinderen: onder de norm van het laboratorium, rekening houdend met een aan de leeftijd gekoppelde controlepopulatie.

Die hypogammaglobulinemie moet tot gevolg hebben gehad dat er ernstige recidiverende infecties zijn opgetreden of chronische bacteriële infecties die gedocumenteerd zijn en waarvoor herhaaldelijk, gepaste en gerichte antibioticatherapie noodzakelijk was. De vergoeding wordt geweigerd als de IgG/IgG₂/IgG₃-deficiëntie te wijten is aan een chronische behandeling met corticosteroïden bijvoorbeeld bij chronisch obstructief longlijden of het gevolg is van verlies via de darm of de urine.

2) congenitale antipolysaccharide antistofdeficiëntie die tot gevolg heeft dat recidive-ren-de infecties zijn opgetreden waarvoor herhaaldelijk antibioticatherapie noodzakelijk was. Deze deficiëntie moet gedocumenteerd zijn door het falen van de antilichaamproductie na pneumococcenvaccinatie.

2. Myeloom en CLL met ernstige secundaire hypogammablobulinemie en recidiverende infecties.

3. Ter behandeling van kinderen die niet ouder zijn dan 18 jaar en lijden aan AIDS.

4. Idiopatische trombocytopenische purpura:

- bij kinderen;
- bij volwassenen met een hoog risico op bloedingen of die wachten op een nakende heelkundige ingreep;

5. Syndroom van Guillain-Barré bij patiënten met één van de volgende

Sandoglobuline

La spécialité est remboursable s'il est démontré qu'elle a été utilisée dans une des situations suivantes:

1. Syndromes d'immunodéficience primaires:

1) agammaglobulinémie ou hypogammaglobulinémie congénitale ou acquise dont soit la teneur totale en IgG, soit la teneur en IgG₂ ou IgG₃ est la suivante:

- adultes : taux d'IgG < 7,50 g/l ; taux d'IgG₂ < 1,50 g/l ; taux d'IgG₃ < 0,20 g/l.

- enfants : valeur inférieure à la norme du laboratoire en tenant compte d'une population de contrôle appariée à l'âge.

Cette hypogammaglobulinémie doit avoir eu pour conséquence la survenue d'infections récurrentes graves ou d'infections bactériennes chroniques, documentées et qui ont nécessité une antibiothérapie répétée et ciblée appropriée. Le remboursement est refusé si la déficience en IgG/IgG₂-/IgG₃ est due à un traitement chronique avec des corticostéroïdes par exemple comme dans la bronchopneumopathie chronique obstructive ou est le résultat d'une perte intestinale ou par les urines.

2) déficience congénitale en anticorps antipolysaccharides qui a comme conséquence que des infections récidivantes sont apparues pour lesquelles une antibiothérapie était nécessaire. Cette déficience doit être documentée par l'échec de la production d'anti-corps après vaccination par les pneumocoques.

2. Myélome et CLL avec hypogammaglobulinémie secondaire sévère et infections récidivantes.

3. Traitement d'enfants n'ayant pas dépassé l'âge de 18 ans et atteints de SIDA.

4. Purpura thrombocytopénique idiopathique:

- chez des enfants;
- chez des adultes qui présentent un grand risque d'hémorragies ou chez ceux qui sont en attente d'une intervention chirurgicale imminente;

5. Syndrome de Guillain-Barré chez les patients qui présentent un des

symptomen:

- progressieve parese (de patiënt kan niet meer dan 10 meter onafhankelijk lopen);
- aanwijzingen van een respiratoire aandoening (klinische observatie of aangetoond door meting van de vitale capaciteit aan het bed van de patiënt);
- tekens van bucco-faryngeale parese.

6. Ziekte van Kawasaki.

7. Preventie van infecties bij patiënten die een allogene beenmergtransplantatie ondergaan.

8. Ter behandeling van Streptokokken toxische shock syndroom.

9. Ter behandeling van sepsis optredend bij prematuoren en in de neonatale periode.

10. Ter behandeling van ernstige multifocale motroneuropathie (MMN) met geleidingsblok, ten gevolge van een geïsoleerd of overheersend motorisch gebrek ter hoogte van de tastzin van tenminste één lidmaat. Deze aandoening moet minstens al twee maanden aanwezig zijn en geen spontane positieve evolutie vertonen. Dit motorisch gebrek moet verantwoordelijk zijn voor een verstoring van de dagelijkse handelingen (schrijven of wijziging in het hanteren van gebruikelijke voorwerpen, moeilijkheid tot stappen) en deze verstoring mag niet vergezeld zijn van evolutieve ontoereikende motorische signalen, ter hoogte van het verlengde merg en die meerdere spieren omvat.

De terugbetaling wordt toegekend voor zover :

De diagnose is bevestigd door een elektromyografisch onderzoek dat een gehele of gedeeltelijke motorische geleidingsblok aantoont en dit buiten de gebruikelijke compressie zones (de cubitale zenuw in de elleboog, de heup-knieholte zenuw extern aan het hoofd van het kuitbeen):

ofwel een ernstige blokkering (vermindering met minstens 50% van de amplitude van het motorisch potentieel) met klinische signalen die overeenstemmen met het bezenewingsgebied van minstens één motoneuron;

ofwel een ‘matige’ blokkering (vermindering met minstens 30% van de amplitude van het motorisch potentieel) in tenminste twee motoneuronen.

Gedurende een eerste periode van 6 maanden, wordt voor het bepalen van

symptômes suivants:

- parésie progressive (le patient ne peut marcher plus de 10 mètres indépendamment);
- signes d'une atteinte respiratoire (observée cliniquement ou démontrée par la capacité vitale au lit du patient);
- signes de parésie bucco-pharyngée.

6. Maladie de Kawasaki.

7. Prévention des infections chez des patients subissant une transplantation allogène de moelle osseuse.

8. Le traitement du syndrome du choc toxique d'origine streptococcique.

9. Le traitement de la septicémie chez des prématurés et pendant la période néonatale.

10. Le traitement de la neuropathie motrice multifocale (NMM) grave avec bloc de conduction, entraînant un déficit moteur isolé ou prédominant par rapport à l'atteinte sensitive, concernant au moins un membre, ayant débuté depuis au moins deux mois et dont l'évolution n'est pas spontanément favorable. Ce déficit moteur doit être responsable d'une perturbation des gestes de la vie quotidienne (écriture ou altération de la manipulation d'objets, trouble de la marche), et ne peut pas être accompagné, dans le territoire bulbaire, de signes moteurs déficitaires évolutifs, qui concerneait plusieurs muscles.

Le remboursement est accordé pour autant que :

Le diagnostic est confirmé lors d'un examen électromyographique avec démonstration de blocs de conduction motrice, complets ou partiels, en dehors des sites habituels de compression (nerf cubital au coude, nerf sciatique poplité externe à la tête du péroné) :

soit un bloc sévère (réduction d'au moins 50% de l'amplitude du potentiel moteur) avec signe clinique correspondant au territoire d'innervation d'au moins un nerf moteur ;

soit un bloc modéré (réduction d'au moins 30% de l'amplitude du potentiel moteur) dans au moins deux nerfs moteurs.

Pendant une première période de six mois, le nombre de conditionnements remboursables tiendra compte d'une quantité totale maximum de 9,0 g/kg,



het aantal terugbetaalde verpakkingen rekening gehouden met totale maximum hoeveelheid van 9,0 g/kg, voor het geheel aan kuren in deze periode.

De initiële kuur wordt indien nodig gevuld door onderhoudskuren waarbij de frekwentie en de dosis bepaald worden door de klinische tekens van hervel van de motore uitvalstekens. De frekwentie kan schommelen tussen 3 weken en enkele maanden, de dosis tussen 0,25 en 2,0 g/kg. De terugbetaling van het vervolg van de behandeling voor nieuwe periodes van 6 maanden en voor een maximale dosis van 9g/kg per 6 maanden mag slechts toegekend worden voor zover er om de 6 maanden een nieuwe klinische evaluatie plaatsvindt.

De toelating tot terugbetaling wordt toegekend door de adviserend geneesheer op basis van een gemotiveerd rapport, opgesteld door een geneesheer specialist in de neurologie of neuro-psychiatrie, dat verklaart dat de desbetreffende patiënt voldoet aan de hierboven vermelde vereisten, en die zich er toe verbindt om het protocol van het elektromyografisch onderzoek ter beschikking te houden van de adviserend geneesheer.

11. Ter behandeling van ernstige chronische inflammatoire demyeliserende neuropathie (Chronic Inflammatory Demyelinating Polyneuropathy of CIPD) in het geval van een gedocumenteerde contra-indicatie voor of een onvoldoende werking van een behandeling met corticoïden welke gedurende 6 weken op een optimale wijze toegediend werden. De terugbetaling wordt toegestaan wanneer de patiënt gelijktijdig aan volgende 6 voorwaarden voldoet :

1°) Een significante functionele handicap: wijziging van de stap wanneer de aandoening zich voornamelijk situeert ter hoogte van de onderste ledematen, wijziging aan de handelingen van dagelijks leven wanneer de symptomen meer uitgesproken zijn ter hoogte van de bovenste ledematen. In het geval van tactiele symptomen met een pijnlijk karakter, zal de functionele handicap als significant aanzien worden wanneer deze onvoldoende reageert op een optimaal toegediende behandeling, gedurende ten minste 2 maanden, met aangepast chronisch analgeticum (clonazepam, carbamazepine, oxcarbazepine, gabapentine, gabapentine of tricyclische derivaten).

2°) Aanwezigheid van een stabiele of progressief sensitief motorisch tekort (zonder een gunstige spontane evolutie) met een motorische of sensoriële overheersing van meer dan één lidmaat, dat reeds minimum 2 maand

pour l'ensemble des cures de cette période.

La cure initiale sera suivie si nécessaire de cures d'entretien dont la fréquence et la dose dépendent des signes cliniques de récidive du déficit moteur. La fréquence varie entre 3 semaines et quelques mois, la dose entre 0,25 et 2,0 g/kg. Le remboursement de la poursuite du traitement pour de nouvelles périodes de 6 mois et pour une dose maximale de 9 g/kg par 6 mois pourra être accordé pour autant que soit réalisée au moins tous les six mois une nouvelle évaluation clinique.

L'autorisation de remboursement sera accordée par le médecin-conseil sur base d'un rapport motivé, établi par un médecin spécialiste en neurologie ou en neuropsychiatrie, qui atteste que le patient concerné remplit toutes les conditions visées ci-dessus, et qui s'engage à tenir à la disposition du médecin-conseil le protocole de l'examen électromyographique.

11. Le traitement de la polyradiculoneuropathie démyélinisante inflammatoire chronique (Chronic Inflammatory Demyelinating Polyneuropathy ou CIDP) sévère, en cas de contre-indication documentée ou d'inefficacité d'un traitement par corticoïdes, administrés de façon optimale pendant au moins 6 semaines. Le remboursement est accordé pour autant que le patient concerné remplies simultanément les 6 conditions suivantes:

1°) Handicap fonctionnel significatif : altération de la marche lorsque l'atteinte prédomine aux membres inférieurs, altération des gestes de la vie quotidienne lorsque les signes sont plus marqués aux membres supérieurs. En présence de manifestations sensitives essentiellement douloureuses, le handicap fonctionnel sera considéré comme significatif lorsqu'un traitement antalgique chronique adapté (clonazepam, carbamazépine, oxcarbazépine, gabapentine ou dérivés tricycliques), administré de façon optimale pendant plus de 2 mois s'est avéré insuffisamment efficace.

2°) Présence d'un déficit sensitivo-moteur, à prédominance sensitive ou motrice, de plus d'un membre, stable ou progressif (sans évolution spontanément favorable), s'étant installé sur une période d'un minimum de 2 mois.

3°) Présence d'une hypo- ou aréflexie ostéotendineuse.

4°) Présence de signes neurophysiologiques de démyélinisation dans au moins 2 nerfs (ralentissement de la vitesse de conduction motrice inférieure de plus de 20% aux valeurs normales, allongement de la latence des ondes F

aanwezig is.

3°) Aanwezigheid van een osteotendineuze hypo- of areflexie.

4°) Aanwezigheid van neurofysiologische tekens van demyelinisatie in tenminste 2 zenuwen (vertraging van de motore geleidingssnelheid minder dan 20% onder de ondergrens van de normale waarden, verlenging van de F golf latentie méér dan 20% boven de bovengrens van de normale waarden, een volledig of gedeeltelijk (vermindering met minstens 30% van de amplitude van de samengestelde spieractiepotentiaal) motoor geleidingsblok buiten de gebruikelijke compressiezones (de ulnaris zenuw ter hoogte van de elleboog, de peroneus zenuw ter hoogte van de fibulakop).

5°) Cellulorachie lager dan 15 witte bloedcellen/mm³ in het geval van een negatieve HIV-serologie of lager dan 50/mm³ indien de HIV serologie positief is.

6°) Formeel uitsluiten, ofwel door anamnese ofwel door klinisch onderzoek van enige andere demyeliniserende neuropathie rekeninghoudende met het geheel aan klinische of neuropathologische anomalieën.

Gedurende een eerste periode van 6 maanden, wordt voor het bepalen van het aantal terugbetaalde verpakkingen rekening gehouden met totale maximum hoeveelheid van 9,0 g/kg, voor het geheel aan kuren in deze periode.

De initiële kuur wordt indien nodig gevolgd door onderhoudskuren waarvan de frekwentie en de dosis bepaald worden door de klinische tekens van hervel van de motore uitvalstekens. De frekwentie kan schommelen tussen 3 weken en enkele maanden, de dosis tussen 0,25 en 2,0 g/kg.

De terugbetaling van het vervolg van de behandeling voor nieuwe periodes van 6 maanden en voor een maximale dosis van 9g/kg per 6 maanden mag slechts toegekend worden voor zover er om de 6 maanden een nieuwe klinische evaluatie van functionele handicap van de CIDP zoals vermeld onder punt 1° hierboven, plaatsvindt.

De toelating tot terugbetaling wordt toegekend door de adviserend geneesheer op basis van een gemotiveerd rapport, opgesteld door een geneesheer specialist in de neurologie of neuro-psychiatrie, dat verklaart dat de desbetreffende patiënt voldoet aan de hierboven vermelde vereisten, en die zich er toe verbindt om het resultaat van het cellulorachie onderzoek en het protocol van het elektromyografisch onderzoek ter beschikking te houden

supérieur de plus de 20% aux valeurs normales, bloc de conduction motrice, complet ou partiel (réduction d'au moins 30% de l'amplitude du potentiel moteur), en dehors des sites habituels de compression (nerf cubital au coude, nerf sciatique poplité externe à la tête du péroné).

5°) Cellulorachie inférieure à 15 globules blancs/mm³ si la sérologie VIH est négative ou inférieure à 50/mm³, si la sérologie VIH est positive.

6°) Exclusion formelle, via une anamnèse et un examen clinique réalisés de façon exhaustive, de toute autre neuropathie démyelinisante pouvant rendre compte de l'entièreté des anomalies cliniques et/ou neurophysiologiques.

Pendant une première période de six mois, le nombre de conditionnements remboursables tiendra compte d'une quantité totale maximum de 9,0 g/kg, pour l'ensemble des cures de cette période.

La cure initiale sera suivie si nécessaire de cures d'entretien dont la fréquence et la dose dépendent des signes cliniques de récidive du déficit moteur. La fréquence varie entre 3 semaines et quelques mois, la dose entre 0,25 et 2,0 g/kg.

Le remboursement de la poursuite du traitement pour de nouvelles périodes de 6 mois et pour une dose maximale de 9 g/kg par 6 mois pourra être accordé pour autant que soit réalisée au moins tous les six mois une nouvelle évaluation clinique du handicap fonctionnel de la CIDP, telle qu'elle est mentionnée au point 1° ci-dessus.

L'autorisation de remboursement sera accordée par le médecin-conseil sur base d'un rapport circonstancié, établi par un médecin spécialiste en neurologie ou en neuropsychiatrie, qui atteste que le patient concerné remplit toutes les conditions visées ci-dessus, et qui s'engage à tenir à la disposition du médecin-conseil le résultat de l'examen de la cellulorachie, et le protocole de l'examen électromyographique.

Le remboursement simultané de la spécialité avec des spécialités à base d'immunoglobulines (groupes de remboursement A-21 et A-78) n'est jamais autorisé.



van de adviserend geneesheer.

De gelijktijdige terugbetaling van de specialiteit met andere specialiteiten op basis van immunoglobulinen (vergoedingsgroepen A-21 en A-78) wordt nooit toegestaan.

Chapter IV	§ 3 200 000
Immunoglobulins:	Multigam

De specialiteit is vergoedbaar indien aangetoond wordt dat ze voor één van de volgende indicaties werd aangewend:

1. Primaire immuundeficiëntiesyndromen:
 - 1) aangeboren of verworven agammaglobulinemie of hypogammaglobulinemie waarbij, ofwel het totale IgG-gehalte ofwel het IgG₂- ofwel het IgG₃-gehalte, als volgt verlaagd zijn:
 - volwassenen: IgG-gehalte < 7,50 g/l; IgG₂-gehalte < 1,50 g/l; IgG₃-gehalte < 0,20 g/l.
 - kinderen: onder de norm van het laboratorium, rekening houdend met een aan de leeftijd gekoppelde controlepopulatie.
 - Die hypogammaglobulinemie moet tot gevolg hebben gehad dat er ernstige recidiverende infecties zijn opgetreden of chronische bacteriële infecties die gedocumenteerd zijn en waarvoor herhaaldelijk, gepaste en gerichte antibioticatherapie noodzakelijk was. De vergoeding wordt geweigerd als de IgG/IgG₂/IgG₃-deficiëntie te wijten is aan een chronische behandeling met corticosteroïden bijvoorbeeld bij chronisch obstructief longlijden of het gevolg is van verlies via de darm of de urine.
 - 2) congenitale antipolysaccharide antistofdeficiëntie die tot gevolg heeft dat recidiverende infecties zijn opgetreden waarvoor herhaaldelijk antibiotica-therapie noodzakelijk was. Deze deficiëntie moet gedocumenteerd zijn door het falen van de antilichaampreductie na pneumococcenvaccinatie.
 2. Myeloom en CLL met ernstige secundaire hypogammablobulinemie en recidiverende infecties.
 3. Ter behandeling van kinderen die niet ouder zijn dan 18 jaar en lijden aan AIDS.
- La spécialité est remboursable s'il est démontré qu'elle a été utilisée dans une des situations suivantes:
 1. Syndromes d'immunodéficience primaires:
 - 1) agammaglobulinémie ou hypogammaglobulinémie congénitale ou acquise dont soit la teneur totale en IgG, soit la teneur en IgG₂ ou IgG₃ est la suivante :
 - adultes : taux d'IgG < 7,50 g/l ; taux d'IgG₂ < 1,50 g/l ; taux d'IgG₃ < 0,20 g/l.
 - enfants : valeur inférieure à la norme du laboratoire en tenant compte d'une population de contrôle appariée à l'âge.
 - Cette hypogammaglobulinémie doit avoir eu pour conséquence la survenue d'infections récurrentes graves ou d'infections bactériennes chroniques, documentées et qui ont nécessité une antibiothérapie répétée et ciblée appropriée. Le remboursement est refusé si la déficience en IgG/IgG₂/IgG₃ est due à un traitement chronique avec des corticostéroïdes par exemple comme dans la bronchopneumopathie chronique obstructive ou est le résultat d'une perte intestinale ou par les urines.
 - 2) déficience congénitale en anticorps antipolysaccharides qui a comme conséquence que des infections récidivantes sont apparues pour lesquelles une antibiothérapie était nécessaire. Cette déficience doit être documentée par l'échec de la production d'anticorps après vaccination par les pneumocoques.
 2. Myélome et CLL avec hypogammaglobulinémie secondaire sévère et infections récidivantes.
 3. Traitement d'enfants n'ayant pas dépassé l'âge de 18 ans et atteints de

4. Idiopatische trombocytopenische purpura:

- bij kinderen;
- bij volwassenen met een hoog risico op bloedingen of die wachten op een nakende heelkundige ingreep;

5. Syndroom van Guillain-Barré bij patiënten met één van de volgende symptomen:

- progressieve parese (de patiënt kan niet meer dan 10 meter onafhankelijk lopen);
- aanwijzingen van een respiratoire aandoening (klinische observatie of aangetoond door meting van de vitale capaciteit aan het bed van de patiënt);
- tekens van bucco-faryngeale parese.

6. Ziekte van Kawasaki.

7. Preventie van infecties bij patiënten die een allogene beenmergtransplantatie ondergaan.

8. Ter behandeling van ernstige multifocale motorneuropathie (MMN) met geleidingsblok, ten gevolge van een geïsoleerd of overheersend motorisch gebrek ter hoogte van de tastzin van tenminste één lidmaat. Deze aandoening moet minstens al twee maanden aanwezig zijn en geen spontane positieve evolutie vertonen. Dit motorisch gebrek moet verantwoordelijk zijn voor een verstoring van de dagelijkse handelingen (schrijven of wijziging in het hanteren van gebruikelijke voorwerpen, moeilijkheid tot stappen) en deze verstoring moet niet vergezeld zijn van evolutieve ontoereikende motorische signalen, ter hoogte van het verlengde merg en die meerdere spieren omvat.

De terugbetaling wordt toegekend voor zover :

De diagnose is bevestigd door een elektromyografisch onderzoek dat een gehele of gedeeltelijke motorische geleidingsblok aantoont en dit buiten de gebruikelijke compressie zones (de cubitale zenuw in de elleboog, de heup-knieholte zenuw extern aan het hoofd van het kuitbeen):

ofwel een ernstige blokkering (vermindering met minstens 50% van de amplitude van het motorisch potentieel) met klinische signalen die overeenstemmen met het bezenuwingsgebied van minstens één motoneuron;

ofwel een ‘matige’ blokkering (vermindering met minstens 30% van de

SIDA.

4. Purpura thrombocytopénique idiopathique:

- chez des enfants;
- chez des adultes qui présentent un grand risque d'hémorragies ou chez ceux qui sont en attente d'une intervention chirurgicale imminente;

5. Syndrome de Guillain-Barré chez les patients qui présentent un des symptômes suivants:

- parésie progressive (le patient ne peut marcher plus de 10 mètres indépendamment);
- signes d'une atteinte respiratoire (observée cliniquement ou démontrée par la capacité vitale au lit du patient);
- signes de parésie bucco-pharyngée.

6. Maladie de Kawasaki.

7. Prévention des infections chez des patients subissant une transplantation allogène de moelle osseuse.

8. Le traitement de la neuropathie motrice multifocale (NMM) grave avec bloc de conduction, entraînant un déficit moteur isolé ou prédominant par rapport à l'atteinte sensitive, concernant au moins un membre, ayant débuté depuis au moins deux mois et dont l'évolution n'est pas spontanément favorable. Ce déficit moteur doit être responsable d'une perturbation des gestes de la vie quotidienne (écriture ou altération de la manipulation d'objets, trouble de la marche), et ne peut pas être accompagné, dans le territoire bulbaire, de signes moteurs déficitaires évolutifs, qui concerneit plusieurs muscles.

Le remboursement est accordé pour autant que :

Le diagnostic est confirmé lors d'un examen électromyographique avec démonstration de blocs de conduction motrice, complets ou partiels, en dehors des sites habituels de compression (nerf cubital au coude, nerf sciatique poplité externe à la tête du péroné) :

soit un bloc sévère (réduction d'au moins 50% de l'amplitude du potentiel moteur) avec signe clinique correspondant au territoire d'innervation d'au moins un nerf moteur ;

soit un bloc modéré (réduction d'au moins 30% de l'amplitude du potentiel moteur) dans au moins deux nerfs moteurs.



amplitude van het motorisch potentieel) in tenminste twee motoneuronen.

Gedurende een eerste periode van 6 maanden, wordt voor het bepalen van het aantal terugbetaalde verpakkingen rekening gehouden met totale maximum hoeveelheid van 9,0 g/kg, voor het geheel aan kuren in deze periode.

De initiële kuur wordt indien nodig gevolgd door onderhoudskuren waarbij de frekwentie en de dosis bepaald worden door de klinische tekens van herval van de motore uitvalstekens. De frekwentie kan schommelen tussen 3 weken en enkele maanden, de dosis tussen 0,25 en 2,0 g/kg. De terugbetaling van het vervolg van de behandeling voor nieuwe periodes van 6 maanden en voor een maximale dosis van 9g/kg per 6 maanden mag slechts toegekend worden voor zover er om de 6 maanden een nieuwe klinische evaluatie plaatsvindt.

De toelating tot terugbetaling wordt toegekend door de adviserend geneesheer op basis van een gemotiveerd rapport, opgesteld door een geneesheer specialist in de neurologie of neuro-psychiatrie, dat verklaart dat de desbetreffende patiënt voldoet aan de hierboven vermelde vereisten, en die zich er toe verbindt om het protocol van het elektromyografisch onderzoek ter beschikking te houden van de adviserend geneesheer.

9. Ter behandeling van ernstige chronische inflammatoire demyeliserende neuropathie (Chronic Inflammatory Demyelinating Polyneuropathy of CIDP) in het geval van een gedocumenteerde contra-indicatie voor of een onvoldoende werking van een behandeling met corticoïden welke gedurende 6 weken op een optimale wijze toegediend werden. De terugbetaling wordt toegestaan wanneer de patiënt gelijktijdig aan volgende 6 voorwaarden voldoet:

1°) Een significante functionele handicap: wijziging van de stap wanneer de aandoening zich voornamelijk situeert ter hoogte van de onderste ledematen, wijziging aan de handelingen van dagelijks leven wanneer de symptomen meer uitgesproken zijn ter hoogte van de bovenste ledematen. In het geval van tactiele symptomen met een pijnlijk karakter, zal de functionele handicap als significant aanzien worden wanneer deze onvoldoende reageert op een optimaal toegediende behandeling, gedurende ten minste 2 maanden, met aangepast chronisch analgeticum (clonazepam, carbamazepine, oxcarbazepine, gabapentine, gabapentine of tricyclische derivaten).

Pendant une première période de six mois, le nombre de conditionnements remboursables tiendra compte d'une quantité totale maximum de 9,0 g/kg, pour l'ensemble des cures de cette période.

La cure initiale sera suivie si nécessaire de cures d'entretien dont la fréquence et la dose dépendent des signes cliniques de récidive du déficit moteur. La fréquence varie entre 3 semaines et quelques mois, la dose entre 0,25 et 2,0 g/kg. Le remboursement de la poursuite du traitement pour de nouvelles périodes de 6 mois et pour une dose maximale de 9 g/kg par 6 mois pourra être accordé pour autant que soit réalisée au moins tous les six mois une nouvelle évaluation clinique.

L'autorisation de remboursement sera accordée par le médecin-conseil sur base d'un rapport motivé, établi par un médecin spécialiste en neurologie ou en neuropsychiatrie, qui atteste que le patient concerné remplit toutes les conditions visées ci-dessus, et qui s'engage à tenir à la disposition du médecin-conseil le protocole de l'examen électromyographique.

9. Le traitement de la polyradiculoneuropathie démyélinisante inflammatoire chronique (Chronic Inflammatory Demyelinating Polyneuropathy ou CIDP) sévère, en cas de contre-indication documentée ou d'inefficacité d'un traitement par corticoïdes, administrés de façon optimale pendant au moins 6 semaines. Le remboursement est accordé pour autant que le patient concerné remplisse simultanément les 6 conditions suivantes:

1°) Handicap fonctionnel significatif : altération de la marche lorsque l'atteinte prédomine aux membres inférieurs, altération des gestes de la vie quotidienne lorsque les signes sont plus marqués aux membres supérieurs. En présence de manifestations sensitives essentiellement douloureuses, le handicap fonctionnel sera considéré comme significatif lorsqu'un traitement antalgique chronique adapté (clonazepam, carbamazépine, oxcarbazépine, gabapentine ou dérivés tricycliques), administré de façon optimale pendant plus de 2 mois s'est avéré insuffisamment efficace.

2°) Présence d'un déficit sensitivo-moteur, à prédominance sensitive ou motrice, de plus d'un membre, stable ou progressif (sans évolution spontanément favorable), s'étant installé sur une période d'un minimum de 2 mois.

3°) Présence d'une hypo- ou aréflexie ostéotendineuse.

4°) Présence de signes neurophysiologiques de démyélinisation dans au

2°) Aanwezigheid van een stabiele of progressief sensitief motorisch tekort (zonder een gunstige spontane evolutie) met een motorische of sensoriële overheersing van meer dan één lidmaat, dat reeds minimum 2 maand aanwezig is.

3°) Aanwezigheid van een osteotendineuze hypo- of areflexie.

4°) Aanwezigheid van neurofysiologische tekens van demyelinisatie in tenminste 2 zenuwen (vertraging van de motore geleidingssnelheid minder dan 20% onder de ondergrens van de normale waarden, verlenging van de F golf latentie méér dan 20% boven de bovengrens van de normale waarden, een volledig of gedeeltelijk (vermindering met minstens 30% van de amplitude van de samengestelde spieractiepotentiaal) motoor geleidingsblok buiten de gebruikelijke compressiezones (de ulnaris zenuw ter hoogte van de elleboog, de peroneus zenuw ter hoogte van de fibulakop).

5°) Cellulorachie lager dan 15 witte bloedcellen/mm³ in het geval van een negatieve HIV-serologie of lager dan 50/mm³ indien de HIV serologie positief is.

6°) Formeel uitsluiten, ofwel door anamnese ofwel door klinisch onderzoek van enige andere demyeliniserende neuropathie rekening houdende met het geheel aan klinische of neuropathologische anomalieën.

Gedurende een eerste periode van 6 maanden, wordt voor het bepalen van het aantal terugbetaalde verpakkingen rekening gehouden met totale maximum hoeveelheid van 9,0 g/kg, voor het geheel aan kuren in deze periode. De initiële kuur wordt indien nodig gevolgd door onderhoudskuren waarvan de frekwentie en de dosis bepaald worden door de klinische tekens van hervall van de motore uitvalstekens. De frekwentie kan schommelen tussen 3 weken en enkele maanden, de dosis tussen 0,25 en 2,0 g/kg. De terugbetaling van het vervolg van de behandeling voor nieuwe periodes van 6 maanden en voor een maximale dosis van 9g/kg per 6 maanden mag slechts toegekend worden voor zover er om de 6 maanden een nieuwe klinische evaluatie van functionele handicap van de CIDP zoals vermeld onder punt 1° hierboven, plaatsvindt.

De toelating tot terugbetaling wordt toegekend door de adviserend geneesheer op basis van een gemotiveerd rapport, opgesteld door een geneesheer specialist in de neurologie of neuro-psychiatrie, dat verklaart dat

moins 2 nerfs (ralentissement de la vitesse de conduction motrice inférieure de plus de 20% aux valeurs normales, allongement de la latence des ondes F supérieur de plus de 20% aux valeurs normales, bloc de conduction motrice, complet ou partiel (réduction d'au moins 30% de l'amplitude du potentiel moteur), en dehors des sites habituels de compression (nerf cubital au coude, nerf sciatique poplité externe à la tête du péroné).

5°) Cellulorachie inférieure à 15 globules blancs/mm³ si la sérologie VIH est négative ou inférieure à 50/mm³, si la sérologie VIH est positive.

6°) Exclusion formelle, via une anamnèse et un examen clinique réalisés de façon exhaustive, de toute autre neuropathie démyélinisante pouvant rendre compte de l'entièreté des anomalies cliniques et/ou neurophysiologiques.

Pendant une première période de six mois, le nombre de conditionnements remboursables tiendra compte d'une quantité totale maximum de 9,0 g/kg, pour l'ensemble des cures de cette période. La cure initiale sera suivie si nécessaire de cures d'entretien dont la fréquence et la dose dépendent des signes cliniques de récidive du déficit moteur. La fréquence varie entre 3 semaines et quelques mois, la dose entre 0,25 et 2,0 g/kg. Le remboursement de la poursuite du traitement pour de nouvelles périodes de 6 mois et pour une dose maximale de 9 g/kg par 6 mois pourra être accordé pour autant que soit réalisée au moins tous les six mois une nouvelle évaluation clinique du handicap fonctionnel de la CIDP, telle qu'elle est mentionnée au point 1° ci-dessus.

L'autorisation de remboursement sera accordée par le médecin-conseil sur base d'un rapport circonstancié, établi par un médecin spécialiste en neurologie ou en neuropsychiatrie, qui atteste que le patient concerné remplit toutes les conditions visées ci-dessus, et qui s'engage à tenir à la disposition du médecin-conseil le résultat de l'examen de la cellulorachie, et le protocole de l'examen électromyographique.

Le remboursement simultané de la spécialité avec des spécialités à base d'immunoglobulines (groupes de remboursement A-21 et A-78) n'est jamais autorisé.



de desbetreffende patiënt voldoet aan de hierboven vermelde vereisten, en die zich er toe verbindt om het resultaat van het cellularachie onderzoek en het protocol van het elektromyografisch onderzoek ter beschikking te houden van de adviserend geneesheer.

De gelijktijdige terugbetaling van de specialiteit met andere specialiteiten op basis van immunoglobulinen (vergoedingsgroepen A-21 en A-78) wordt nooit toegestaan.

Chapter IV

§ 3 210 000

Immunoglobulins:

De specialiteit is vergoedbaar indien aangetoond wordt dat ze voor één van de volgende indicaties werd aangewend:

1. Primaire immuundeficiëntiesyndromen:

1) aangeboren of verworven agammaglobulinemie of hypogammaglobulinemie waarbij, ofwel het totale IgG gehalte ofwel het IgG₂- ofwel het IgG₃-gehalte, als volgt verlaagd zijn:

- volwassenen: IgG gehalte < 7,50 g/l; IgG₂-gehalte < 1,50 g/l; IgG₃-gehalte < 0,20 g/l.
- kinderen: onder de norm van het laboratorium, rekening houdend met een aan de leeftijd gekoppelde controlepopulatie.

Die hypogammaglobulinemie moet tot gevolg hebben gehad dat er ernstige recidiverende infecties zijn opgetreden of chronische bacteriële infecties die gedocumenteerd zijn en waarvoor herhaaldelijk, gepaste en gerichte antibioticatherapie noodzakelijk was. De vergoeding wordt geweigerd als de IgG/IgG₂/IgG₃-deficiëntie te wijten is aan een chronische behandeling met corticosteroïden bijvoorbeeld bij chronisch obstructief longlijden of het gevolg is van verlies via de darm of de urine.

2) Congenitale antipolysaccharide antistofdeficiëntie die tot gevolg heeft dat recidiverende infecties zijn opgetreden waarvoor herhaaldelijk antibioticatherapie noodzakelijk was. Deze deficiëntie moet gedocumenteerd zijn door het falen van de antilichaamproductie na pneumococcenvaccinatie.

2. Myeloom en CLL met ernstige secundaire hypogammablobulinemie en

Kiovig, Nanogam, Octagam, Privigen

La spécialité est remboursable s'il est démontré qu'elle a été utilisée dans une des situations suivantes:

1. Syndromes d'immunodéficience primaires:

1) agammaglobulinémie ou hypogammaglobulinémie congénitale ou acquise dont soit la teneur totale en IgG, soit la teneur en IgG₂ ou IgG₃ est la suivante :

- adultes : taux d'IgG < 7,50 g/l ; taux d'IgG₂ < 1,50 g/l ; taux d'IgG₃ < 0,20 g/l.

- enfants : valeur inférieure à la norme du laboratoire en tenant compte d'une population de contrôle appariée à l'âge.

Cette hypogammaglobulinémie doit avoir eu pour conséquence la survenue d'infections récurrentes graves ou d'infections bactériennes chroniques, documentées et qui ont nécessité une antibiothérapie répétée et ciblée appropriée. Le remboursement est refusé si la déficience en IgG/IgG₂/IgG₃ est due à un traitement chronique avec des corticostéroïdes par exemple comme dans la bronchopneumopathie chronique obstructive ou est le résultat d'une perte intestinale ou par les urines.

2) Déficience congénitale en anticorps antipolysaccharides qui a comme conséquence que des infections récidivantes sont apparues pour lesquelles une antibiothérapie était nécessaire. Cette déficience doit être documentée par l'échec de la production d'anticorps après vaccination par les pneumocoques.



recidiverende infecties.

3. Ter behandeling van kinderen die niet ouder zijn dan 18 jaar en lijden aan AIDS.

4. Idiopatische trombocytopenische purpura:

- bij kinderen;
- bij volwassenen met een hoog risico op bloedingen of die wachten op een nakende heelkundige ingreep;

5. Syndroom van Guillain-Barré bij patiënten met één van de volgende symptomen:

- progressieve parese (de patiënt kan niet meer dan 10 meter onafhankelijk lopen);
- aanwijzingen van een respiratoire aandoening (klinische observatie of aangetoond door meting van de vitale capaciteit aan het bed van de patiënt);
- tekens van bucco-faryngeale parese.

6. Ziekte van Kawasaki.

7. Preventie van infecties bij patiënten die een allogene beenmergtransplantatie ondergaan.

De gelijktijdige terugbetaling van de specialiteit met andere specialiteiten op basis van immunoglobulinen (vergoedingsgroepen A-21 en A-78) wordt nooit toegestaan.

2. Myélome et CLL avec hypogammaglobulinémie secondaire sévère et infections récidivantes.

3. Traitement d'enfants n'ayant pas dépassé l'âge de 18 ans et atteints de SIDA.

4. Purpura thrombocytopénique idiopathique:

- chez des enfants;
- chez des adultes qui présentent un grand risque d'hémorragies ou chez ceux qui sont en attente d'une intervention chirurgicale imminente;

5. Syndrome de Guillain-Barré chez les patients qui présentent un des symptômes suivants:

- parésie progressive (le patient ne peut marcher plus de 10 mètres indépendamment);
- signes d'une atteinte respiratoire (observée cliniquement ou démontrée par la capacité vitale au lit du patient);
- signes de parésie bucco-pharyngée.

6. Maladie de Kawasaki.

7. Prévention des infections chez des patients subissant une transplantation allogène de moelle osseuse.

Le remboursement simultané de la spécialité avec des spécialités à base d'immunoglobulines (groupes de remboursement A-21 et A-78) n'est jamais autorisé.



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