

# SURVEILLANCE DE LA SÉCURITÉ VACCINALE EN BELGIQUE : PLACE ET LIMITES D'UNE APPROCHE REPOSANT SUR LES TAUX DE BASE





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## ■ PRÉFACE

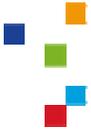
Le cerveau humain n'est pas très habile à manier les probabilités. Et, comme nous le révèlent les études des psychologues, il l'est encore moins lorsque ces probabilités s'appliquent à des phénomènes rares voire très rares. Cela ne fait pas beaucoup de différence que l'on parle d'une chance de un sur cinq mille ou d'une chance de un sur cinq-cents mille : à partir du moment où nous pouvons nous représenter plus ou moins clairement ce qui se passerait si cela nous arrivait, nous surestimons quasi inévitablement cette probabilité. A fortiori si il s'agit de l'une ou l'autre catastrophe que nous voulons éviter à tout prix. Les compagnies d'assurance s'empressent d'ailleurs d'exploiter la chose.

Certaines mesures de prévention, comme la vaccination, semblent être particulièrement vulnérables à cette problématique. A chaque (nouvelle) campagne de vaccination émergent çà et là des « victimes » du vaccin fortement médiatisées, ce qui engendre bien souvent des conséquences dramatiques pour la couverture vaccinale. Rien ne sert d'accuser les relayers de l'information, car en la matière les médias suivent leur propre logique. Rien ne sert non plus de lutter contre certaines réactions excessives où certains affabulent en criant au complot. Lorsqu'elles soutiennent de nouvelles mesures de prévention, les autorités ont simplement le devoir de fournir toutes les garanties nécessaires afin que la nouvelle mesure ne comporte pas de risques déraisonnables et que les avantages de cette mesure dépassent de loin les potentiels inconvénients ou complications.

Il faut donc procéder en trois étapes : 1) il faut pouvoir détecter à quel moment la fréquence d'un certain problème devient anormalement élevée. Il faut 2) connaître la fréquence normale de cette complication au sein d'une population non vaccinée – on parle du taux de base. Et finalement il faut 3) savoir qui est vacciné. Tout ceci est plus facilement dit que fait car cela s'applique à des manifestations indésirables très rares.

La question de recherche qui nous a été soumise par l'Agence Fédérale des Médicaments et Produits de Santé est d'évaluer dans quelle mesure la Belgique peut apporter une réponse adéquate au deuxième défi, à savoir le calcul des taux de base. Est-ce qu'un pays aussi petit que la Belgique peut fournir des chiffres valables ou est-il plus judicieux de jouer la carte de l'Europe ? Les réponses apportées sont plutôt nuancées. Le dernier mot n'est certainement pas dit ici, mais nous espérons toutefois avoir pu apporter une pierre à l'édifice de cette importante question de société.

Raf MERTENS  
Directeur Général



## ■ RÉSUMÉ

## INTRODUCTION

La surveillance de la sécurité postvaccinale fait référence à la détection, l'évaluation, la compréhension et la prévention des manifestations postvaccinales indésirables (MAPI). Le rôle d'un programme de surveillance de la sécurité vaccinale est d'identifier les signaux de sécurité dont l'évaluation plus poussée peut mener à la découverte de MAPI précédemment non identifiées, non reconnues ou encore insuffisamment comprises. Le principe de base de la détection est une analyse des effets observés/attendus : le nombre de manifestations indésirables observées dans le groupe vacciné est comparé au nombre auquel on aurait pu s'attendre s'il n'y avait pas eu d'association. Si le taux des manifestations indésirables dans la population vaccinée s'avère significativement supérieur au nombre attendu, un signal de sécurité est émis et une évaluation plus poussée de ce signal s'avère nécessaire pour évaluer un éventuel lien de causalité. Il existe plusieurs manières de calculer le nombre attendu des manifestations postvaccinales indésirables. Une manière courante de le faire consiste à extrapoler le taux d'incidence d'une maladie dans la population générale (c.-à-d. le taux de base) à la population des personnes vaccinées.

Ce rapport évalue la pertinence et la faisabilité de l'approche reposant sur le taux de base dans le cadre de la surveillance de la sécurité vaccinale en Belgique. La principale question de recherche que nous avons donc abordée ici est celle de la faisabilité du calcul et de l'utilisation des taux de base des manifestations indésirables dans l'évaluation des problèmes de sécurité dans le cadre de la vaccination à grande échelle en Belgique.

Pour aborder cette question, nous avons commencé par dresser un aperçu des différentes sources de données pouvant être utilisées pour calculer le taux de base des maladies sélectionnées en Belgique et nous avons résumé leurs potentiels et leurs limitations. Ensuite, nous avons fait une tentative pilote d'estimation des taux de base d'un certain nombre de maladies en Belgique. Enfin, nous avons décrit la surveillance postvaccinale en Belgique et nous avons dressé un aperçu des difficultés et des pistes d'amélioration.



## BASES DE DONNÉES POUVANT FOURNIR LES TAUX DE BASE EN BELGIQUE

### Sources de données administratives

Le Résumé Clinique Minimum et le Résumé Hospitalier Minimum (RCM-RHM) sont transmis par les hôpitaux au Service Public Fédéral Santé publique (SPF SP) dans le cadre du financement des hôpitaux. Cet ensemble de données pourrait servir à calculer le taux de base. Toutefois, il convient d'en reconnaître certaines limitations. Premièrement, cet ensemble de données ne contient pas d'information sur les soins ambulatoires, ce qui signifie que les épisodes morbides qui ne donnent pas lieu à une hospitalisation ne sont pas détectés. Deuxièmement, cet ensemble de données ne permet pas de faire la distinction entre les premières admissions et les réadmissions pour les mêmes épisodes morbides. Troisièmement, un phénomène décrit comme le "DRG creep", c'est-à-dire la surévaluation systématique et délibérée de la sévérité du case mix pour maximiser le financement hospitalier peut constituer un biais important dans l'évaluation des taux de base de certaines maladies ce qui a été notamment démontré en Belgique pour la thrombocytopenie. Quatrièmement, bien que le transfert des données soit effectué en théorie tous les 6 mois, on note actuellement un retard d'environ 2 ans. Cinquièmement, l'âge précis du patient n'est pas disponible étant donné qu'on ne dispose que de son année de naissance, ce qui représente une difficulté majeure dans l'évaluation des taux de base pour le groupe d'âge le plus vacciné, celui des bébés. Enfin, le diagnostic n'est pas encodé par le médecin traitant et n'est ni revu, ni validé dans la majorité des bases de données administratives.

CARENET est une plate-forme Internet sécurisée qui permet l'échange d'informations entre les hôpitaux et les compagnies d'assurance santé à propos des hospitalisations individuelles : moment de l'admission, durée du séjour à l'hôpital, diagnostic et procédures médicales pour lesquels le remboursement est prévu par l'INAMI. Le principal objectif de CARENET est de simplifier et d'accélérer le transfert de ces données. CARENET peut donc présenter l'avantage de donner plus rapidement accès à des données sur certaines maladies spécifiques que ne le permet le RCM. Il convient néanmoins de faire remarquer que le champ diagnostique est

alphanumérique, ce qui permet donc d'introduire du texte ou les codes CIM-9-CM. L'interview des informateurs clés a révélé que la validité des données fournies par les différents hôpitaux est probablement extrêmement variable. Certains hôpitaux introduisent les mêmes données CIM-9-CM que celles introduites dans la base de donnée du RCM et cette tâche est confiée à des encodeurs professionnels. Dans d'autres hôpitaux, ce champ est rempli par du personnel clinique non spécialisé essentiellement sous la forme de texte libre. Dans ce dernier cas, des techniques de « text mining » sont nécessaires pour extraire et analyser les données. Il convient également de mentionner que la seule obligation légale consiste à remplir le champ de diagnostic, pas à le remplir avec des données précises et complètes, et qu'il n'y a pas de contrôle de qualité sur le diagnostic. CARENET présente également la même limitation que le RCM, celle d'être actuellement limité uniquement aux patients hospitalisés.

En Belgique, chaque décès donne lieu à la délivrance d'un certificat de décès établi par un médecin et sur lequel figure(nt) la/les cause(s) du décès. Pour chaque décès, plusieurs diagnostics sont indiqués conformément aux règles internationales de l'OMS et aux codes CIM-10: principale cause de décès (principal), causes immédiates, intermédiaires et associées.

### Réseaux sentinelles

En Belgique, deux réseaux vigies de MG sont actifs. Le premier est organisé par l'Institut de Santé Publique (ISP) depuis 1978 et regroupe actuellement près de 200 médecins généralistes (MG), représentant environ 1,8% de l'ensemble des médecins généralistes belges. Ce réseau a prouvé sa fiabilité en tant que système de surveillance d'un large éventail de données épidémiologiques liées à la santé, comme par exemple le diabète, l'accident vasculaire cérébral, le cancer, et les accidents même si peu de ces éléments ont pu, jusqu'à présent, être liés à des MAPI. Quoi qu'il en soit, la liste des maladies surveillées est révisée chaque année et l'inclusion de nouveaux signaux de sécurité potentiels pourrait être demandée par les instances sanitaires publiques.



Le deuxième, Intego est un réseau vigie volontaire qui regroupe des MG de Flandre (1,05% des MG regroupés dans 55 pratiques) coordonné par le département de médecine générale de la Katholieke Universiteit Leuven. Les taux d'incidents sont publiés sur un site web sur la base des codes ICPC2 (International Classification of Primary Care), par an et par groupe d'âge.

Ces deux réseaux sentinelles présentent un certain nombre de limitations. La première est que la population couverte n'est pas connue avec précision, ce qui rend le calcul des taux de base imprécis. La deuxième, la population couverte est relativement peu importante et insuffisante pour obtenir des estimations stables des taux de base des événements relativement rares. La troisième limitation importante réside dans le fait que ces réseaux fournissent des informations relatives aux pratiques de MG sans tenir compte des soins hospitaliers. Ce problème pourrait être partiellement compensé par l'enregistrement systématique du feedback des soignants hospitaliers sur les patients hospitalisés à leur MG mais on ne peut pas clairement établir dans quelle mesure cette façon de procéder mènerait à des estimations fiables.

PediSurv (Pediatric diseases Surveillance), créé en 2002 par l'ISP est un réseau de surveillance auquel participent des pédiatres belges (n=504; 35% de l'ensemble des pédiatres) et des MG bruxellois (n=354; 36% des MG bruxellois). Son objectif est principalement d'étudier les affections infectieuses rares chez l'enfant et de surveiller l'impact des mesures de santé publique telle que la vaccination dans ce groupe. Jusqu'ici, aucune MAPI n'a été reprise sur la liste. Pedisurv possède néanmoins, en théorie, les capacités potentielles de surveiller les manifestations indésirables rares sévères : la possibilité d'inclure les intussusceptions a récemment été discutée. En termes d'accès aux données, les données de Pedisurv peuvent être demandées par l'IPS mais une convention doit être signée. Les rapports annuels sont disponibles à l'adresse <https://www.wiv-isp.be/pedisurv/>.

## ESTIMATION DES TAUX DE BASE: UNE ÉTUDE PILOTE

Nous avons essayé d'estimer l'incidence d'un certain nombre de maladies qui pourraient servir de taux de base afin d'évaluer la faisabilité du processus et explorer les problèmes et les biais rencontrés. Dans cette étude pilote, nous nous sommes concentrés sur trois MAPI graves potentielles, à savoir la mort subite du nourrisson, le syndrome de Guillain-Barré et les crises d'épilepsie.

Nous avons montré que pour un certain nombre de maladies, il est possible de produire des taux de base en relative concordance avec les taux de manifestations observées dans d'autres pays. Le caractère exhaustif des registres des décès est quasi certain et la précision du diagnostic « mort subite du nourrisson » devrait augmenter progressivement suite à la promulgation, en 2003, d'une loi imposant de procéder à une autopsie sur tous les enfants de moins de 18 mois décédés de mort subite du nourrisson. Le calcul des taux de base à partir des données du RCM s'est également prouvé faisable, dans certains cas, à condition qu'il soit lié à une maladie spécifique menant systématiquement à une hospitalisation notamment le syndrome de Guillain-Barré et uniquement si l'on tient compte du diagnostic principal. Toutefois, les données du RCM n'ont pas pour objectif premier d'être utilisées à des fins épidémiologiques.



## SURVEILLANCE DE LA SÉCURITÉ VACCINALE EN BELGIQUE

En Belgique, la pharmacovigilance ressortit à la responsabilité légale du division vigilance l'AFMPS, une agence du SPF Santé publique. Fondamentalement, si une approche reposant sur le taux de base devait être mise en place, ce serait l'AFMPS qui serait chargé d'établir le nombre des MAPI observées.

L'AFMPS reçoit des rapports individuels des professionnels de la santé (médecins, pharmaciens, dentistes, infirmières, sagefemmes) et des rapports de cas individuels des titulaires des autorisations de mise sur le marché (TAMM), c'est-à-dire, des sociétés pharmaceutiques. Les titulaires des autorisations de mise sur le marché informés d'un effet indésirable grave, par les professionnels de la santé, par les investigateurs des essais cliniques ou encore par le biais des publications scientifiques, doivent le rapporter au AFMPS dans un délai de 7 ou 15 jours (dépendant de la situation) à compter de la prise de connaissance de l'information. Les promoteurs des essais cliniques doivent également rapporter tous les effets indésirables graves et inattendus (EIGI) observés pendant l'essai clinique, et ce pour les médicaments aussi bien avec que sans autorisation de mise sur le marché. Pour les effets indésirables non graves le délai est de 90 jours. D'autres sources de rapports individuels sont également en place depuis peu:

- les citoyens sont également invités à rapporter les MAPI directement au AFMPS.
- Vaccinet, un système de commande en ligne de tous les vaccins de Flandre, opérationnel depuis 2004. Il permet également d'obtenir désormais des informations supplémentaires sur les effets indésirables attendus, mais on ne sait pas dans quelle mesure cette option est déjà utilisée.

Nous avons passé en revue les données relatives aux vaccins collectées par l'AFMPS depuis 2008. Le tableau 1 illustre le nombre de MAPI attendu rapporté au AFMPS par an (en 2012, la période d'enregistrement ne couvrait que la moitié de l'année). Le chiffre annuel avoisine 200 rapports par an. Un pic a été observé en 2009 qui est principalement dû aux rapports sur les effets indésirables du Pandemrix, le vaccin utilisé pendant la pandémie de grippe. Comme on peut le voir, le nombre de rapports est très peu élevé ceci du fait qu'il s'agit des effets indésirables rapportés pour l'ensemble des vaccins administrés en Belgique.

**Tableau 1: Nombre de réactions indésirables attendu suite à la vaccination, rapporté au AFMPS de 2008 à mi-2012**

Année	Nombre
2008	216
2009	352
2010	170
2011	208
2012	85
<b>Total</b>	<b>1031</b>



## DISCUSSION ET CONCLUSION

Nous avons montré qu'en Belgique, il est possible de calculer le taux de base d'un certain nombre de maladies. Bien que la fiabilité de ces taux de base ne soit pas connue avec précision, il est probable qu'elle soit relativement élevée pour le taux calculé sur la base du principal diagnostic des maladies bien définies nécessitant une hospitalisation systématique ou sur les causes de décès enregistrées sur le certificat de décès. Le système belge actuel de collecte des données est trop fragmenté pour permettre un calcul fiable des taux de base d'autres maladies.

Toutefois, même si l'on peut fournir des taux de base raisonnablement fiables, les défis relatifs à leur utilisation réelle ne peuvent pas actuellement être tous relevés en Belgique. Les deux défis importants actuels sont le sous-rapportage des réactions indésirables aux autorités compétentes et la relativement petite taille de la population des personnes vaccinées en Belgique. Le défi que représente cette dernière caractéristique est impossible à relever et souligne la nécessité de mettre en place une surveillance de la sécurité vaccinale au niveau européen. Cette surveillance européenne se développe d'ailleurs rapidement.

Étant donné ces éléments, il ne semble pas approprié d'investir dans le développement d'une approche de la surveillance vaccinale en Belgique reposant sur le taux de base. Cela ne veut certainement pas dire pour autant que la surveillance de la sécurité vaccinale soit une voie sans issue. L'amélioration de la déclaration des MAPI au AFMPS est essentielle. La déclaration directe des MAPI par les consommateurs, qui sera bientôt réalité, pourrait représenter un grand pas en avant dans cette direction. L'amélioration des pratiques de déclaration par les prestataires de soins et une classification plus standardisée des MAPI représentent également d'importants objectifs dans ce cadre. Une analyse et une interprétation rapides des signaux de sécurité potentiels renvoyés par l'EMA ou d'autres sources revêtent une importance cruciale dans le cadre d'une communication et d'une minimisation appropriées des risques.

L'étude de la possibilité de mettre en place d'autres stratégies de surveillance de sécurité vaccinale en Belgique n'entraîne pas dans le cadre du présent projet. De telles stratégies, devraient être basées sur une évaluation globale des besoins en informations sanitaires en Belgique et proposer une collecte des données et un plan d'analyse globaux. Il convient toutefois de noter que le data mining est déjà effectué par l'EMA à partir d'EudraVigilance, un ensemble de données qui comprend les rapports de sécurité envoyés au AFMPS. Des études de cohorte et des séries de cas auto-contrôlés pourraient également être mises en place par le biais de l'utilisation de l'ensemble des données de l'AMI (Agence InterMutualiste) qui contient des informations à la fois sur certains types de vaccination et sur l'incidence des hospitalisations, des décès et du recours à des services sanitaires ou des médicaments spécifiques. La faisabilité d'une telle approche demande une évaluation plus approfondie.



## ■ RECOMMANDATIONS<sup>a</sup>

### *Au Ministre de la Santé Publique et à l'AFMPS :*

- Etant donné les faiblesses du système d'information sanitaire actuel en Belgique et la taille limitée de la population, nous ne recommandons pas d'investir dans la détection systématique de signaux de sécurité suivant l'approche des taux de base.
- Cette détection des signaux de sécurité devrait préférentiellement s'inscrire au niveau Européen (à travers l'Agence Européenne du Médicament) et la Belgique doit y contribuer en fournissant des données sur les effets indésirables potentiels. Nous recommandons donc de prendre des mesures pour renforcer cette déclaration par les prestataires de soins et les consommateurs au niveau national; la nouvelle plate-forme Internet de déclaration des effets indésirables à l'AFMPS offre l'opportunité de progresser à ce niveau. Ces mesures devraient être basées sur une évaluation des barrières à la déclaration des effets indésirables en Belgique.
- Au delà de la détection des signaux de sécurité, le calcul des taux de base d'un nombre limité d'effets indésirables graves peut s'avérer utile au niveau national, dans le cadre de la communication du risque, lors de la survenue d'événements attribués à des problèmes de sécurité vaccinale qui inquiètent le public. Cela peut être le cas des morts subites du nourrisson ou des maladies particulièrement invalidantes telles que le syndrome de Guillain-Barré.
- D'autres approches de type cohorte prospective pour évaluer l'association entre les vaccins et certains événements indésirables à travers des bases de données existantes (par ex. données de remboursement) - qui n'ont pas fait l'objet de ce rapport - pourraient être investiguées.

### *Agenda de recherche*

- La faisabilité du recours à d'autres techniques de détection des signaux de sécurité en Belgique, plus efficaces et plus puissantes que l'analyse du ratio entre les événements observés vs attendus abordée dans ce rapport, devrait être étudiée de manière plus approfondie. Ces techniques comprennent les études cas-témoins ou encore l'analyse des séries de cas auto-contrôlés.

<sup>a</sup> Le KCE reste seul responsable des recommandations adressées aux autorités publiques





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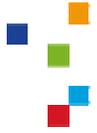
ABBREVIATION	DEFINITION
ACIP	Advisory Committee on Immunization Practices
ADROI	Adverse Drug Reactions On-line Information Tracking
AE	Adverse event
AEFI	Adverse effect following immunization
AFP	Acute flaccid paralysis
ARIMA	Autoregressive integrated moving average
ASR	Annual Safety Report
BC	Brighton 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	Geïntegreerd 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

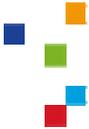


## ■ SYNTHÈSE

### 1 INTRODUCTION

La surveillance de la sécurité postvaccinale fait référence à la détection, l'évaluation, la compréhension et la prévention des manifestations postvaccinales indésirables (MAPI). Le rôle d'un programme de surveillance de la sécurité vaccinale est d'identifier les signaux de sécurité dont l'évaluation plus poussée peut mener à la découverte de MAPI précédemment non identifiées, non reconnues ou encore insuffisamment comprises. Cela peut être le cas, notamment, pour les MAPI dont la fréquence est trop faible pour être détectée dans les études de pré-homologation réalisées sur des échantillons de taille limitée. Les MAPI peuvent également être dues à des effets pharmacologiques précédemment non reconnus du vaccin, des interactions médicamenteuses ou vaccinales, des facteurs liés à certaines populations spécifiques de patients, des facteurs individuels liés aux patients (notamment des facteurs pharmacogénomiques). Des épisodes morbides et la vaccination peuvent également s'avérer coïncidents, c'est-à-dire ne pas présenter de relation de cause à effet.

Une mauvaise interprétation des effets indésirables qui ne sont que temporairement liés à une vaccination peut donner lieu à une préoccupation publique importante sur la sécurité vaccinale et gravement porter atteinte à la confiance du public dans les programmes de vaccination. La surveillance de la sécurité vaccinale revêt donc une importance cruciale pour la santé publique. Elle permet aussi de surveiller l'équilibre risque/bénéfice de la vaccination et de déclencher le processus décisionnel approprié lorsque cet équilibre n'est plus considéré comme favorable. Enfin, elle offre une base objective pour étayer les messages destinés à rassurer la population et les praticiens lorsque des associations entre des vaccins et des maladies coïncidentes sont publiées et soulèvent des doutes par rapport aux dangers de la vaccination.



### 1.1 Différentes approches de détection des signaux

La surveillance de la sécurité peut être passive, active, ou les deux à la fois en fonction de la manière dont est organisée la collecte des données. La surveillance passive repose sur le rapport spontané des effets indésirables, tandis que la surveillance active repose sur la collecte prospective d'événements vaccinaux et d'événements indésirables. Le principe de base de la détection de signaux de sécurité reste toutefois quasi similaire dans les deux types de surveillance : le nombre de manifestations indésirables observées dans le groupe vacciné est comparé au nombre auquel on aurait pu s'attendre s'il n'y avait pas eu d'association. Si le taux des manifestations indésirables dans la population vaccinée s'avère significativement supérieur au nombre attendu, un signal de sécurité est émis et une évaluation plus poussée de ce signal s'avère nécessaire pour évaluer un éventuel lien de causalité. Il existe plusieurs manières de calculer le nombre attendu des manifestations postvaccinales indésirables. Une manière courante de le faire consiste à extrapoler le taux d'incidence d'une maladie dans la population générale (c.-à-d. le taux de base) à la population des personnes vaccinées. Le nombre de manifestations indésirables observées (O) dans la population vaccinée est ensuite comparé au nombre attendu (E). Un rapport O/E significativement plus élevé que 1 constitue un signal de sécurité. C'est ce que l'on appelle l'approche du taux de base, qui constitue aussi le sujet de ce rapport. D'autres méthodes de détection des signaux de sécurité comprennent le data mining et les études de cohorte.

### 1.2 Objectif de l'étude

Ce rapport évalue la pertinence et la faisabilité de l'approche reposant sur le taux de base dans le cadre de la surveillance de la sécurité vaccinale en Belgique. L'agence fédérale des médicaments et des produits de santé (Federal Agency for Medicines and Health Products - AFMPS) a soumis cette question au KCE parce qu'elle est confrontée à des rapports de manifestations postvaccinales indésirables qui pourraient être soit réelles, soit des artéfacts. Quel que soit le caractère de ces manifestations indésirables, cette agence se doit de rapidement prendre les mesures appropriées par rapport aux programmes de vaccination et à la communication du risque. Il n'y a pas, actuellement, en Belgique, de surveillance de la sécurité postvaccinale et les méthodes de data mining sont rarement utilisées. L'approche reposant sur le taux de base pourrait donc être amenée à jouer un rôle central à ce niveau. Toutefois, pour l'instant, ces données de base de ne sont généralement pas disponibles pour la Belgique. La principale question de recherche que nous avons donc abordée ici est celle de la faisabilité du calcul et de l'utilisation des taux de base de certains problèmes de santé dans l'évaluation des problèmes de sécurité lors d'une vaccination à grande échelle en Belgique.

Pour aborder cette question, nous avons commencé par dresser un aperçu des différentes sources de données pouvant être utilisées pour calculer le taux de base des maladies sélectionnées en Belgique et nous avons résumé leurs potentiels et leurs limitations. Ensuite, nous avons fait une tentative pilote d'estimation des taux de base d'un certain nombre de maladies en Belgique. Enfin, nous avons décrit la surveillance postvaccinale en Belgique et nous avons dressé un aperçu des difficultés et des pistes d'amélioration.



## 2 BASE DE DONNÉE PERMETTANT DE FOURNIR LE TAUX DE BASE EN BELGIQUE

### 2.1 Sources de données administratives

#### 2.1.1 *Le résumé clinique minimum (RCM)*

Le Résumé Clinique Minimum (RCM) et le Résumé Hospitalier Minimum (RHM) sont transmis par les hôpitaux au Service Public Fédéral Santé publique (SPF SP) dans le cadre du financement des hôpitaux. Ces données contiennent la synthèse de chaque séjour à l'hôpital : les données démographiques du patient, des données administratives sur certaines données liées aux séjours hospitaliers ainsi que des données diagnostiques codées à l'aide d'un chiffre repris dans les codes de l'ICM-9-CM. Cet ensemble de données pourrait servir à calculer le taux de base. Toutefois, il convient d'en reconnaître certaines limitations. Premièrement, cet ensemble de données ne contient pas d'information sur les soins ambulatoires, ce qui signifie que les épisodes morbides qui ne donnent pas lieu à une hospitalisation ne sont pas détectés. Deuxièmement, cet ensemble de données ne permet pas de faire la distinction entre les premières admissions et les réadmissions pour les mêmes épisodes morbides. Troisièmement, un phénomène décrit comme le "DRG creep", c'est-à-dire la surévaluation systématique et délibérée de la sévérité du case mix pour maximiser le financement hospitalier peut constituer un biais important dans l'évaluation des taux de base de certaines maladies ce qui a été notamment démontré en Belgique pour la thrombocytopenie. Quatrièmement, bien que le transfert des données soit effectué en théorie tous les 6 mois, on note actuellement un retard d'environ 2 ans. Cinquièmement, l'âge précis du patient n'est pas disponible étant donné qu'on ne dispose que de son année de naissance, ce qui représente une difficulté majeure dans l'évaluation des taux de base pour le groupe d'âge le plus vacciné, celui des bébés. Enfin, le diagnostic n'est pas encodé par le médecin traitant et n'est ni revu, ni validé dans la majorité des bases de données administratives.

#### 2.1.2 *CARENET*

CARENET est une plate-forme Internet sécurisée qui permet l'échange d'informations entre les hôpitaux et les compagnies d'assurance santé à propos des hospitalisations individuelles : moment de l'admission, durée du séjour à l'hôpital, diagnostic et procédures médicales pour lesquels le remboursement est prévu par l'INAMI. Le principal objectif de CARENET est de simplifier et d'accélérer le transfert de ces données. CARENET peut donc présenter l'avantage de donner plus rapidement accès à des données sur certaines maladies spécifiques que ne le permet le RCM. Il convient néanmoins de faire remarquer que le champ diagnostique est alphanumérique, ce qui permet donc d'introduire du texte ou les codes CIM-9-CM. L'interview des informateurs clés a révélé que la validité des données fournies par les différents hôpitaux est probablement extrêmement variable. Certains hôpitaux introduisent les mêmes données CIM-9-CM et RCM et cette tâche est confiée à des encodeurs professionnels. Dans d'autres hôpitaux, ce champ est rempli par le personnel clinique essentiellement sous la forme de texte libre. Dans ce dernier cas, des techniques de text mining sont nécessaires pour extraire et analyser les données. Il convient également de mentionner que la seule obligation légale consiste à remplir le champ de diagnostic, pas à le remplir avec des données précises et complètes, et qu'il n'y a pas de contrôle de qualité sur le diagnostic. CARENET présente également la même limitation que le RCM, celle d'être actuellement limité uniquement aux patients hospitalisés.



### 2.1.3 Registre des décès

En Belgique, chaque décès donne lieu à la délivrance d'un certificat de décès établi par un médecin et sur lequel figure(nt) la/les cause(s) du décès. Pour chaque décès, plusieurs diagnostics sont indiqués conformément aux règles internationales de l'OMS et aux codes CIM-10: principale cause de décès (principal), causes immédiates, intermédiaires et associées. Les données relatives aux causes de décès peuvent être demandées par chaque communauté et une convention doit être signée. Selon les Communautés on dispose de données sur les causes de décès de juin 2012, 2009 ou 2010 (retard d'1-2 ans). La Flandre publie aussi des données brutes sur son site web. Les données nationales sont disponibles, par exemple, sur le site web du SPF Économie (<http://statbel.fgov.be/en/statistics/figures/>) ou sur le site web de l'ISP (<https://www.wiv-isp.be/epidemi/spma/>), mais pour ces données, le retard est plus important (environ 3 ans) et en septembre 2012, les données les plus récentes dataient de 2008. Les limitations de cette base de données n'ont pas été étudiées ; on constate toutefois que les données collectées sur la mort subite montrent des différences au niveau des pratiques de codage entre les différentes régions.

Au niveau supranational, le projet Euro-MOMO (monitoring of mortality-surveillance de la mortalité) est un projet financé par l'UE, lancé en 2008 et coordonné par le Statens Serum Institut au Danemark, qui a mis en place un système de surveillance de la mortalité toute cause (brute) dans 20 pays de l'UE, y compris la Belgique. L'objectif de ce projet est de détecter en temps réel, le nombre exagéré de décès liés à la grippe ou à d'autres éventuelles menaces de santé publique dans l'UE.

## 2.2 Réseaux sentinelles

### 2.2.1 Réseaux de MG

En Belgique, deux réseaux vigies de MG sont actifs. Le premier est organisé par l'Institut de Santé Publique (ISP) depuis 1978 et regroupe actuellement près de 200 médecins généralistes (MG), représentant environ 1,8% de l'ensemble des médecins généralistes belges. Ce réseau a prouvé sa fiabilité en tant que système de surveillance d'un large éventail de données épidémiologiques liées à la santé, comme par exemple le diabète, l'accident vasculaire cérébral, le cancer, et les accidents même si peu de ces éléments ont pu, jusqu'à présent, être liés à des MAPI. Quoi qu'il en soit, la liste des maladies surveillées est révisée chaque année et l'inclusion de nouveaux signaux de sécurité potentiels pourrait être demandée par les instances sanitaires publiques.

Le deuxième, Intego est un réseau vigie volontaire qui regroupe des MG de Flandre (1,05% des MG regroupés dans 55 pratiques) coordonné par le département de médecine générale de la Katholieke Universiteit Leuven. Les taux d'incidents sont publiés sur un site web sur la base des codes ICPC2<sup>a</sup>, par an et par groupe d'âge.

Ces deux réseaux sentinelles pourraient être utiles dans le calcul des taux de base. Toutefois, ils présentent un certain nombre de limitations. La première est que la population couverte n'est pas connue avec précision, ce qui rend le calcul des taux de base imprécis. La deuxième, la population couverte est relativement peu importante et insuffisante pour obtenir des estimations stables des taux de base des événements relativement rares. La troisième limitation importante réside dans le fait que ce réseau fournit des informations relatives aux pratiques de MG sans tenir compte des soins hospitaliers. Ce problème pourrait être partiellement compensé par l'enregistrement systématique du feedback des soignants hospitaliers sur les patients hospitalisés à leur MG mais on ne peut pas clairement établir dans quelle mesure cette façon de procéder mènerait à des estimations fiables.

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<sup>a</sup> International Classification of Primary Care



### 2.2.2 *Pedisurv*

PediSurv (Pediatric diseases Surveillance), créé en 2002 par l'ISP est un réseau de surveillance auquel participent des pédiatres belges (n=504; 35% de l'ensemble des pédiatres) et des MG bruxellois (n=354; 36% des MG bruxellois). Son objectif est principalement d'étudier les affections infectieuses rares chez l'enfant et de surveiller l'impact des mesures de santé publique telle que la vaccination dans ce groupe. Ce système de surveillance repose sur une base volontaire mais il est demandé à ses participants d'envoyer chaque mois un rapport, même s'ils n'ont pas de cas à rapporter. Pour chaque cas rapporté, un questionnaire est rempli qui contient des informations démographiques, cliniques et vaccinales. La sensibilité de la surveillance de Pedisurv (c'est-à-dire la proportion de tous les cas détectés par le système de surveillance) a été évaluée à 73% pour les infections invasives à pneumocoque en 2005-06 dans le cadre d'une étude de capture-recapture (utilisant 3 sources)<sup>2,3</sup>. En 2012, Pedisurv couvre les maladies suivantes : rougeole, rubéole, oreillons, infection invasive à pneumocoque, paralysie flasque aiguë, syndrome de rubéole congénitale et syndrome hémolytique et urémique. La liste des maladies sous surveillance est évaluée chaque année par un comité de pilotage et mise à jour conformément aux besoins de santé publique. L'ajout de n'importe quelle nouvelle maladie sur la liste tient également compte de la charge de travail liée au rapportage des cas de cette maladie pour les médecins participants. Jusqu'ici, aucune MAPI n'a été reprise sur la liste. Pedisurv possède néanmoins, en théorie, les capacités potentielles de surveiller les manifestations indésirables rares sévères : la possibilité d'inclure les intussusceptions a récemment été discutée. En termes d'accès aux données, les données de Pedisurv peuvent être demandées par l'IPS mais une convention doit être signée. Les rapports annuels sont disponibles à l'adresse <https://www.wiv-isp.be/pedisurv/>.

## 3 ESTIMATION DES TAUX DE BASE : UNE ÉTUDE PILOTE

Nous avons essayé d'estimer l'incidence d'un certain nombre de maladies qui pourraient servir de taux de base afin d'évaluer la faisabilité du processus et explorer les problèmes et les biais rencontrés. Dans cette étude pilote, nous nous sommes concentrés sur trois MAPI graves potentielles, à savoir la mort subite du nourrisson, le syndrome de Guillain-Barré et les crises d'épilepsie.

### 3.1 Mort subite du nourrisson

Dans le monde industrialisé, le syndrome de mort subite du nourrisson constitue la principale cause de décès chez les nourrissons de 1 à 11 mois. Le taux de base des décès par mort subite du nourrisson (MSN) revêt une importance cruciale dans l'évaluation post-commercialisation de la sécurité vaccinale étant donné que les principaux programmes de vaccination du nourrisson coïncident temporairement avec le pic d'âge d'incidence de la MSN. Dans notre approche, nous avons utilisé les registres de décès comme source de données, plus précisément les décès enregistrés par la Fédération de Wallonie-Bruxelles, la Vlaams Agentschap Zorg en Gezondheid et la Région de Bruxelles- Capitale.

**Tableau 1 – Mort subite du nourrisson (code CIM10 R95 comme cause initiale du décès) en Belgique, sur la base des certificats de décès de 2000-2009**

Population / année	Nombre annuel moyen 2000-09	Taux annuel moyen par 1000 naissances vivantes 2000-09	2009 taux par 1000 naissances vivantes	% avec autopsie *
MSN Flandres	26.1	0.41	0.29	60%
MSN Bruxelles	6.5	0.42	0.33	59%
MSN Wallonie	23.0	0.59	0.47	59%
MSN Belgique	55.6	0.47	0.35	59%
Autres causes de décès mal définies et non spécifiées	1.6	0.01	0.01	80%

\* Autopsie en cours ou prévue au moment de l'encodage du décès

Sources : Fédération de Wallonie-Bruxelles, Vlaams Agentschap Zorg en Gezondheid et Région de Bruxelles- Capitale

Les taux calculés à partir des certificats de décès belges sont similaires à ceux calculés dans les statistiques nationales sur les décès dans d'autres pays de l'UE. Des variations régionales sont observées (en Wallonie les taux sont plus élevés), qui peuvent partiellement s'expliquer par des différences au niveau de l'encodage, mais les schémas dans le temps et par âge restent similaires. Les taux montrent une tendance à diminuer ces dernières années tandis que le taux d'autopsie, lui a augmenté depuis l'entrée en vigueur d'une nouvelle loi demandant une autopsie pour établir un diagnostic en cas de mort subite. Les données belges sur les causes de décès semblent constituer un élément approprié pour le calcul des taux de base des décès par mort subite du nourrisson en Belgique. Étant donné les tendances à la baisse observée au fil du temps, les taux les

plus récents doivent être utilisés; ces données sont disponibles au niveau régional avec un retard de 1 à 2 ans.

### 3.2 Syndrome de Guillain-Barré

Le syndrome de Guillain-Barré (SGB) est une maladie démyélinisante inflammatoire aiguë des nerfs périphériques. Son étiologie n'est pas encore clairement élucidée mais on pense qu'il s'agit d'un processus immunitaire, habituellement déclenché par une infection aiguë. Le vaccin constitue un autre facteur potentiel de déclenchement et des associations entre des vaccins et le SGB ont été rapportées, bien que les mécanismes sous-jacents ne soient pas encore élucidés. Le SGB représente donc un élément important de la surveillance de la sécurité vaccinale. Pour cette étude nous avons utilisé l'ensemble des données du RCM.

En moyenne, 550 hospitalisations liées à un SGB (SGB en tant que diagnostic primaire ou secondaire) ont été rapportées sur la période 2004-09, y compris 55% d'hospitalisations avec le SGB comme principal diagnostic. Des admissions répétées (envoi dans un autre hôpital ou réadmission) ont été rapportées pour 25% de l'ensemble des admissions associées à un SGB et 18% des admissions liées à un SGB comme principal diagnostic. Si l'on exclut les admissions répétées, les taux bruts vont de 2,2 à 2,4 par 100 000 pour le SGB en tant que principal diagnostic et de 3,9 à 5,0 par 100 000 pour le SGB tout diagnostic. Les taux bruts du SGB en tant que diagnostic principal sont stables au fil des ans. Le taux d'hospitalisation augmente avec l'âge.

Les données relatives aux patients belges hospitalisés sur la base du RCM en tant que diagnostic primaire montrent des taux légèrement plus élevés que les taux de base rapportés pour le SGB sur l'ensemble des pays d'Europe occidentale mentionnés dans la littérature mais les diagnostics n'ont pas été validés. D'autres études ont montré que des taux reposant sur les données de sortie de l'hôpital - qui ne sont pas validées - surestiment les véritables taux du SGB en raison de l'inclusion d'autres cas. De plus, les erreurs potentielles de mauvais classement des maladies neurologiques chroniques à la première admission et les règles de remboursement des immunoglobulines peuvent également avoir joué un rôle dans la surestimation du nombre des admissions portant le code du SGB en Belgique. Étant donné que les manifestations postvaccinales indésirables (ou "manifestations observées") sont habituellement soumises



à une évaluation et à une vérification du diagnostic, l'estimation des taux de base du SGB basée sur la revue de la littérature régulièrement mise à jour constitue sans doute une meilleure option, plus solide, que des données RCM non validées. Toutefois, les manifestations de SGB "observées" qui seraient invalidées (ou qui ne sont pas encore validées) pourraient être comparées aux taux de base reposant sur les données des RCM belges.

Cet exemple montre également que le comptage de l'ensemble des occurrences d'une maladie donnée dans le cadre du RCM sans différencier le diagnostic primaire et secondaire entraîne une large surestimation des taux de base. Il serait probablement sage de baser le calcul des manifestations uniquement sur le diagnostic primaire, même si on ne connaît pas le taux des cas non détectés lié à cette stratégie.

### 3.3 Epilepsie

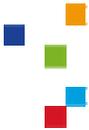
Dans Intego, les incidences rapportées chez les enfants de moins de cinq ans sont de 92/100 000 personnes par an pour les femmes et de 99/100 000 pour les hommes sur la période 2008 – 2010 et les incidences tous groupes d'âge confondus sont de 9/100 000 pour les femmes et de 14/100 000 pour les hommes. Ces taux sont inférieurs à ceux rapportés dans la littérature et reflètent probablement le fait qu'en Belgique, la majorité des crises d'épilepsie ne donne pas lieu à des contacts avec un médecin généraliste, ce qui mène à une sous-estimation.

L'incidence de l'épilepsie standardisée sur l'âge, calculée sur la base des données hospitalières (ensemble des données RCM) va de 120/100 000 personnes par an en 2004 à 112/100 000 en 2009. Ces chiffres sont similaires à ceux des manifestations observées au niveau européen (projet VAESCO). Il vaut la peine de mentionner qu'une augmentation due à la vaccination peut être difficile à détecter si elle repose sur l'ensemble des crises d'épilepsie du fait que les crises d'épilepsie liées à la vaccination sont probablement fébriles, un type de crise ne représentant qu'une part mineure seulement de l'ensemble des crises d'épilepsie rapportée. En tout cas, ces estimations ne peuvent pas être comparées sans plus aux estimations de la littérature, étant donné que les types de crise d'épilepsie et les méthodes de collecte des données sont trop différents.

### 3.4 Faisabilité et fiabilité du calcul des taux de base en Belgique

Nous avons montré que pour un certain nombre de maladies, il est possible de produire des taux de base en relative concordance avec les taux de manifestations observées dans d'autres pays. Le caractère exhaustif du registre des décès est quasi certain et la précision du diagnostic « mort subite du nourrisson » devrait augmenter progressivement suite à la promulgation, en 2003, d'une loi imposant de procéder à une autopsie sur tous les enfants de moins de 18 mois décédés de mort subite du nourrisson. Le calcul des taux de base à partir des données du RCM s'est également prouvé faisable, nonobstant les limitations expliquées dans la section 2.1.1, à condition qu'il soit lié à une maladie spécifique menant systématiquement à une hospitalisation notamment le syndrome de Guillain-Barré et uniquement si l'on tient compte du diagnostic principal. Toutefois, les données du RCM n'ont pas pour objectif premier d'être utilisées à des fins épidémiologiques et les manquements suivants ont été mis en lumière:

- Les maladies de longue durée nécessitant de multiples hospitalisations seront surestimées, étant donné que les hospitalisations répétées ne pourront que partiellement être détectées. Cette situation est liée au fait que les identifiants patient uniques ne sont disponibles que depuis 2004. Le nombre des hospitalisations répétées varie de moins de 5% à 50% en fonction des maladies.
- Les données du RCM font une distinction entre le diagnostic principal et le diagnostic secondaire. Le choix du diagnostic à utiliser est loin d'être évident et le meilleur choix dépend probablement de la maladie concernée. Cela dépend aussi des règles de codage du RCM.
- Le RCM ne contient que les données des patients hospitalisés ce qui ne permet pas de prendre en compte les cas des patients ambulatoires souffrant d'une forme moins sévère de la maladie ne nécessitant pas d'hospitalisation.
- L'optimisation du case mix aux fins de financement peut entraîner une surestimation de certaines maladies. L'ampleur de ce phénomène, et la mesure dans laquelle il influence le codage du diagnostic principal, ne sont pas connues.



- La sensibilité et la spécificité du codage du RCM ne sont pas connues, mais l'évaluation de ces paramètres n'entraîne pas dans le cadre du présent projet. La fiabilité précise des taux de base reposant sur le RCM n'a pas non plus été établie, même s'il est probable qu'elle soit élevée pour certaines maladies spécifiques nécessitant systématiquement une hospitalisation. L'évaluation de cette fiabilité demanderait d'effectuer des études de capture-recapture.

## 4 DÉFIS ET OPPORTUNITÉS DE LA SURVEILLANCE DE LA SÉCURITÉ VACCINALE

### 4.1 Surveillance de la sécurité vaccinale en Belgique

En Belgique, la pharmacovigilance ressortit à la responsabilité légale du SPF Santé publique. Fondamentalement, si une approche reposant sur le taux de base devait être mise en place, ce serait la division vigilance l'AFMPS qui serait chargée d'établir le nombre des MAPI observées.

#### 4.1.1 Collecte des données

Le CBPH reçoit des rapports individuels des professionnels de la santé (médecins, pharmaciens, dentistes) et des rapports de cas individuels des titulaires des autorisations de mise sur le marché (TAMM), c'est-à-dire, des sociétés pharmaceutiques. Les titulaires des autorisations de mise sur le marché informés d'un effet indésirable grave, par les professionnels de la santé, par les investigateurs des essais cliniques ou encore par le biais des publications scientifiques, doivent le rapporter au AFMPS dans un délai de 15 jours à compter de la prise de connaissance de l'information. Les promoteurs des essais cliniques doivent également rapporter tous les effets indésirables graves et inattendus (EIGI) observés pendant l'essai clinique, et ce pour les médicaments aussi bien avec que sans autorisation de mise sur le marché. D'autres sources de rapports individuels sont également en place depuis peu:

- depuis juillet 2012, les citoyens sont également invités à rapporter les MAPI directement au AFMPS.
- Vaccinet, un système de commande en ligne de tous les vaccins de Flandre, opérationnel depuis 2004. Il permet également d'obtenir désormais des informations supplémentaires sur les effets indésirables attendus, mais on ne sait pas dans quelle mesure cette option est déjà utilisée<sup>4</sup>.



En plus des rapports individuels, le AFMPS reçoit également régulièrement des Rapports périodiques sur la sécurité des médicaments (PSUR) à usage humain (DSUR) des TAMM. Ce rapport contient un aperçu et une évaluation de toutes les réactions graves et non graves observées à l'intérieur et à l'extérieur de l'Union européenne. Après 5 ans, un aperçu de synthèse doit être fourni dans le cadre du dossier de renouvellement de l'autorisation de mise sur le marché. Afin d'évaluer la sécurité des médicaments utilisés dans les essais cliniques, le promoteur doit rédiger un rapport annuel de sécurité sur les effets indésirables graves observés pendant l'essai clinique et remettre ce rapport au AFMPS (rapport annuel de sécurité, RAS).

Le AFMPS confie l'évaluation des rapports individuels et de synthèse à des groupes de travail spécifiques. Pour cette tâche, le AFMPS est assisté par une équipe d'experts internes et externes. Pour chaque rapport individuel, le AFMPS évalue le degré de causalité en utilisant les catégories de causalité de l'OMS (certaine, probable, possible, peu probable, non classée, pas de classification possible). Si nécessaire, l'évaluateur peut contacter le notifiant pour obtenir de plus amples informations ou des précisions. Dans le rapport des TAMM ou des investigateurs, l'évaluation de cette causalité est habituellement déjà effectuée.

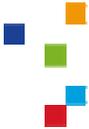
Nous avons passé en revue les données relatives aux vaccins collectées par le AFMPS depuis 2008. Le tableau 2 illustre le nombre de MAPI attendu rapporté au AFMPS par an (en 2012, la période d'enregistrement ne couvrait que la moitié de l'année). Le chiffre annuel avoisine 200 rapports par an. Un pic a été observé en 2009 qui est principalement dû aux rapports sur les effets indésirables du Pandemrix, le vaccin utilisé pendant la pandémie de grippe.

**Tableau 2 – Nombre de réactions indésirables attendu suite à la vaccination, rapporté au AFMPS de 2008 à mi-2012**

Année	Nombre
2008	216
2009	352
2010	170
2011	208
2012	85
<b>Total</b>	<b>1031</b>

La base de données ne contenait qu'un nombre limité de doublons. Les rapports les plus fréquents concernaient le vaccin contre le HPV (Gardasil; 214), le vaccin contre la diphtérie, la coqueluche et le tétanos (Infanrix; 132) et le vaccin contre la grippe pandémique de 2009 (Pandemrix; 93). Un nombre important de rapport de cas se rapportait à plusieurs vaccins ainsi qu'à d'autres médicaments de sorte qu'on n'a pas toujours pu clairement établir à quel vaccin, le cas échéant, attribuer les réactions indésirables potentielles.

En ce qui concerne la description des effets indésirables, pour le classement des informations relatives aux effets indésirables associés à l'utilisation des produits biopharmaceutiques et autres produits médicaux, nous avons utilisé la terminologie médicale de MedDRA (Medical Dictionary for Regulatory Activities). Ce dictionnaire reprend un ensemble de diagnostics et symptômes. On ne sait pas comment les diagnostics ont été déterminés, mais il ne semble pas que des définitions spécifiques (p. ex. la classification de Brighton) des MAPI aient été utilisées. On ne sait pas si et le cas échéant comment les diagnostics ont été vérifiés mais une partie des effets indésirables rapportés au AFMPS n'était clairement pas liée à des vaccins, notamment les métastases pulmonaires, la diarrhée sanguinolente ou la syphilis secondaire. Certains rapports concernaient même des échecs vaccinaux, des problèmes de stockage ou une utilisation inadéquate du produit. L'exploitation de ces données est difficile et demanderait de procéder à un data mining. Toutefois, même en cas



d'enregistrement correct, de vérification adéquate du diagnostic et de data mining approprié, la puissance statistique de toute analyse restera probablement faible étant donné le petit nombre de rapports de cas. Le nombre limité de ces rapports (il est à noter qu'il concerne l'ensemble des vaccins) indique un sous-rapportage important qu'il n'a cependant pas été possible de quantifier.

Pour augmenter le nombre des rapports sur les effets indésirables des médicaments directement transmis au AFMPS par les professionnels de la santé et améliorer la qualité de ce rapport, un projet baptisé « Pharmacovigilance active » a été lancé par le AFMPS en 2008. Une communication annonçant le projet a été publiée dans le Folia Pharmacotheapeutica de janvier 2008 et un appel à participation a été publié sur le site web de l'AFMPS, du CBIP, de plusieurs associations professionnelles et des comités médico-pharmaceutiques. Des séances de sensibilisation ont été organisées dans les hôpitaux, les universités et les associations médicales/pharmaceutiques. Un outil de rapportage en ligne a été développé, une version papier plus conviviale est distribuée via Folia Pharmacotheapeutica depuis mars 2009, un feed-back plus détaillé et individualisé est envoyé au notifiant en réponse à chaque rapport et un bulletin d'information électronique "VIG-news" qui reprend les dernières nouvelles en matière de pharmacovigilance issues de différentes sources est disponible sur le site web de l'AFMPS. Malgré tous ces efforts, on ne note aucune tendance à la hausse au niveau du nombre des rapports.

#### 4.1.2 Analyse des données

Actuellement, le AFMPS ne procède à aucune analyse des données. Tous les rapports de cas individuels sont traités électroniquement et rassemblés dans la base de données EudraVigilance. Cet d'archivage centralisé à l'EMA, regroupe les rapports des effets indésirables attendus liés aux médicaments autorisés dans l'Espace économique européen et aux médicaments étudiés dans le cadre des essais cliniques. Les TAMM et les promoteurs des essais cliniques introduisent directement leurs propres rapports dans la base de données européenne.<sup>b</sup>

L'AFMPS dispose d'un accès direct à tous les éléments de données contenus dans EudraVigilance.

Une analyse statistique est effectuée par l'EMA. Sur une base mensuelle, l'EMA procède à un data mining (PRR: Proportional Reporting Ratio) à partir de l'ensemble des données contenues dans Eudravigilance, et répercute les résultats aux agences nationales de pharmacovigilance. L'AFMPS est responsable de l'analyse ultérieure des signaux de sécurité potentiels rapportés par l'EMA concernant 20 produits spécifiques. Cette tâche est effectuée principalement par le biais de l'examen des rapports individuels au cas par cas et la vérification du caractère plausible de l'association entre le vaccin et les MAPI potentielles.

#### 4.2 Limitations et pistes de solution

Le taux de base sert à générer des estimations sur le nombre attendu des effets indésirables chez les personnes vaccinées et à interpréter les signaux de sécurité potentiels en évaluant si le nombre réel des événements observés dépasse ou non le nombre attendu. Le comptage des MAPI et l'analyse du rapport O/E présentent également plusieurs difficultés. Le tableau 3 résume les défis et opportunités à chaque étape d'un système de surveillance de la sécurité vaccinale reposant sur l'utilisation des taux de base.

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<sup>b</sup> [http://www.fagg-afmps.be/nl/MENSELIJK\\_gebruik/geneesmiddelen/geneesmiddelen/geneesmiddelenbewaking/info\\_icsrs\\_-\\_mah\\_sponsors/](http://www.fagg-afmps.be/nl/MENSELIJK_gebruik/geneesmiddelen/geneesmiddelen/geneesmiddelenbewaking/info_icsrs_-_mah_sponsors/)


**Tableau 3 – Défis et opportunités de la surveillance de la sécurité vaccinale reposant sur le taux de base (TB)**

Type	Défis		Options d'amélioration	
	Source		Générales	Spécifiques pour la Belgique
<b>1. Estimation des taux de base en fonction des rapports sur les diagnostics hospitaliers</b>				
<b>1.1. Sous-rapportage</b>	L'enregistrement ne repose que sur les données des patients hospitalisés alors que certaines réactions sont observées chez des patients ambulatoires		<ul style="list-style-type: none"> <li>Mettre l'accent sur la surveillance des effets indésirables graves entraînant l'hospitalisation ou le décès</li> <li>Fusionner les sources de données de la première et de la deuxième ligne des services de santé pour permettre une évaluation complète des événements</li> </ul>	Voir section 3
	Détection sous-optimale de E par absence de définitions standards et/ou procédures diagnostiques		<ul style="list-style-type: none"> <li>Standardiser les définitions de cas et les procédures</li> </ul>	Le plan de CARENET propose d'élargir la surveillance à la première ligne mais la faisabilité et le calendrier de cette proposition ne sont pas rapportés. On ne dispose actuellement d'aucun ensemble de données diagnostiques pour la première ligne.
<b>1.2. Sur-rapportage</b>	Erreurs de codage (DRG creep)		Contrôles/stimulants administratifs	
	Absence de définitions standards et/ou procédures diagnostiques		Standardiser les définitions de cas et les procédures	
<b>1.3. Biais liés à l'exposition</b>	Taux de base mesurés dans une population partiellement exposée (rapport O/E biaisé vers 1)		<ul style="list-style-type: none"> <li>Concentrer la surveillance sur les nouveaux vaccins</li> <li>Mesurer le taux de base dans la population non exposée</li> <li>Tenir compte des biais dans l'analyse</li> </ul>	
<b>1.4. Intemporalité</b>	Retard dans l'accès aux données sur le TB relatif à une autre période, p. ex. O, ce qui représente un problème si le TB varie au fil des ans		Accélérer l'accès aux données	RCM ensemble de données théoriquement disponibles après 6 mois. Le retard diminue progressivement (mais était toujours de 2 ans en 2012). CARENET est plus rapide
			Concentrer la surveillance sur les maladies qui ont un TB stable au fil du temps (p. ex. SGB)	Voir section 3



## 2. Comptage O par surveillance passive

<b>2.1. Sous-rapportage</b>	Rapportage sub-optimal	« Stimuler » les professionnels de la santé à faire des rapports	Le projet « pharmacovigilance active » n'a pas été une grande réussite
		Permettre aux consommateurs de rapporter directement les effets indésirables aux autorités compétentes	Sera bientôt effectif
<b>2.2. Sur-rapportage</b>	Biais de la notoriété : c'est-à-dire que les individus vaccinés rapportent plus souvent des effets indésirables quand les médias attirent leur attention sur ceux-ci	Communication prudente du risque?	
<b>2.3. Vérification différentielle</b>	<ul style="list-style-type: none"> <li>Définitions différentes des événements pour O &amp; TB</li> <li>La vérification de O dans le cadre de la surveillance est plus difficile que celle du taux de base</li> </ul>	Utilisation des mêmes définitions de cas et procédures diagnostiques pour O et E (définitions de Brighton)	

## 3. Comptage des sujets exposés

	L'administration du vaccin n'est pas enregistrée pour tous les vaccins (se base sur l'exposition qui repose sur une surestimation de la vente des vaccins)	Registre vaccinal détaillé	Vaccinet va bientôt être étendu au niveau national et comprendra toutes les catégories d'âge
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## 4. Analyse des données

<b>4.1. Facteurs confondants</b>	Les rapports de cas (O) peuvent concerner des individus présentant des caractéristiques spécifiques liées à la fois aux MAPI et à la vaccination	Standardisation par âge et par sexe. Une standardisation est également possible sur la base d'autres paramètres	
<b>4.2. Petit nombre d'événements*</b>	<ul style="list-style-type: none"> <li>Caractère peu élevé des populations exposées</li> <li>Faible association entre les vaccins et les MAPI</li> </ul>	Développement d'une surveillance transnationale (p. ex. Eudrasurveillance), avec une estimation des taux de base à ce niveau	Le AFMPS transmet déjà les données à Eudravigilance**
<b>4.3. Tests répétés (multiple)</b>	La surveillance de la sécurité est un processus continu	Développer une guidance statistique claire pour tenir compte de cet aspect	

\* Ce qui entraînera une faible puissance statistique et la volatilité du rapport O/E avec un risque de résultats illogiques

\*\* Les données sont utilisées pour le data mining et non pas pour l'analyse du rapport O/E



## 5 UN PAS EN AVANT?

Nous avons montré qu'en Belgique, il est possible de calculer le taux de base d'un certain nombre de maladies. Bien que la fiabilité de ces taux de base ne soit pas connue avec précision, il est probable qu'elle soit relativement élevée pour le taux calculé sur la base du principal diagnostic des maladies bien définies nécessitant une hospitalisation systématique ou sur les causes de décès enregistrées sur le certificat de décès. Le système belge actuel de collecte des données est trop fragmenté pour permettre un calcul fiable des taux de base d'autres maladies.

Toutefois, même si l'on peut fournir des taux de base raisonnablement fiables, les défis relatifs à leur utilisation réelle ne peuvent pas actuellement être tous relevés en Belgique comme le résume le tableau 3. Parmi les défis importants actuels on note le sous-rapportage des réactions indésirables aux autorités compétentes et la relativement petite taille de la population des personnes vaccinées en Belgique. Le défi que représente cette dernière caractéristique est impossible à relever et souligne la nécessité de mettre en place une surveillance de la sécurité vaccinale au niveau européen. Cette surveillance européenne se développe d'ailleurs rapidement.

Étant donné ces éléments, il ne semble pas approprié d'investir dans le développement d'une approche de la surveillance vaccinale en Belgique reposant sur le taux de base. Cela ne veut certainement pas dire pour autant que la surveillance de la sécurité vaccinale soit une voie sans issue. L'amélioration du rapportage des MAPI au AFMPS est essentielle. La déclaration directe des MAPI par les consommateurs, qui sera bientôt réalité, pourrait représenter un grand pas en avant dans cette direction. L'amélioration des pratiques de rapportage par les prestataires de soins et une classification plus standardisée des MAPI représentent également d'importants objectifs dans ce cadre. Une analyse et une interprétation rapides des signaux de sécurité potentiels renvoyés par l'EMA ou d'autres sources revêtent une importance cruciale dans le cadre d'une communication et d'une minimisation appropriées des risques.

L'étude de la possibilité de mettre en place d'autres stratégies de surveillance de sécurité vaccinale en Belgique n'entraîne pas dans le cadre du présent projet. De telles stratégies, devraient être basées sur une évaluation globale des besoins en informations sanitaires en Belgique et proposer une collecte des données et un plan d'analyse globaux. Il convient toutefois de noter que le data mining est déjà effectué par l'EMA à partir d'EudraVigilance, un ensemble de données qui comprend les rapports de sécurité envoyés au AFMPS. Des études de cohorte et des séries de cas auto-contrôlés pourraient également être mises en place par le biais de l'utilisation de l'ensemble des données de l'AMI (Agence InterMutualiste) qui contient des informations à la fois sur certains types de vaccination et sur l'incidence des hospitalisations, des décès et du recours à des services sanitaires ou des médicaments spécifiques. La faisabilité d'une telle approche demande une évaluation plus approfondie.



## ■ 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.<sup>5</sup> 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.<sup>6</sup> 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.<sup>6,7</sup> 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 verificatory action.<sup>8</sup>

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.<sup>9</sup> 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.<sup>10</sup> It simply attempts to identify adverse events that are reported more commonly for one vaccine than others.<sup>11</sup> 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.<sup>12</sup>

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:<sup>13</sup>

**Table 1 – Contingency table**

Health event	Vaccinated		Total
	Yes	No	
Yes	a	b	a+b
No	c	d	c+d
<b>Total</b>	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:<sup>14</sup>

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

We can test whether the observed number of events is significantly different from the number expected with the simple continuity corrected<sup>c</sup>  $\chi^2$  statistic:

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

<sup>c</sup> 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  $\chi^2$  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.<sup>13</sup> 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,<sup>13</sup> 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.<sup>15</sup> 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).<sup>16</sup> 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,<sup>17</sup> or the assessment of increased Kawasaki disease after RotaTeq vaccine.<sup>18</sup>

### 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.<sup>19</sup> It is thus important to define a priori which signals warrant further follow-up, i.e. to define the criteria of an impact analysis.<sup>5</sup> 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.<sup>20</sup> 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).<sup>21</sup> 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.<sup>21</sup>

Priority signals must be evaluated rapidly to determine whether they represent a risk which may warrant further assessment, communication or other risk minimization actions.<sup>5</sup> 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.<sup>5</sup> 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.<sup>5</sup> 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 USA<sup>22</sup>**

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, VAERS 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,<sup>23</sup> 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.<sup>24</sup> 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.<sup>25</sup> 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.<sup>26</sup> 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).<sup>1</sup> 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.<sup>27,28</sup> 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.<sup>29</sup> 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.<sup>29</sup> 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.<sup>8</sup> Use of BCCDs was found more reliable and valid than individual, nonsystematic clinician review.<sup>30</sup> 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 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> 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 China<sup>31</sup> 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.<sup>31</sup> 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<sup>d</sup> and healthcare professionals<sup>e</sup> 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.<sup>32</sup> 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<sup>f</sup>. 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.<sup>9,33</sup> As an example, by linking the US national

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<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.fagg-afmps.be/en/human\\_use/medicines/medicines/pharmacovigilance/data\\_collection\\_evaluation\\_measures/](http://www.fagg-afmps.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.<sup>33</sup>



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%.<sup>33</sup> 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.<sup>29</sup> 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.<sup>17</sup> 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.<sup>34</sup> 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 Iran<sup>35</sup>) and/or the association between the vaccine under scrutiny and the AE is strong. Estimating accurately E in such conditions is thus difficult,<sup>25</sup> hampering a genuine evaluation whether there is significantly more observed adverse events than expected.<sup>23</sup> 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.<sup>h</sup> 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 more details on this registry).

<sup>h</sup> 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 Denmark<sup>34</sup> and Finland,<sup>36</sup> 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 confounding<sup>37</sup>). 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.<sup>14</sup>

#### 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  $j^{\text{th}}$  age group ( $n_j$  being the number of individuals of the cohort in the age-specific group  $j$  and  $\lambda_j$  being the background rate in that age specific group  $j$ ):

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

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.<sup>13</sup> 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.<sup>14</sup> 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.<sup>38</sup> 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).<sup>13</sup>

**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.<sup>15</sup> 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.<sup>14</sup>

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  $\alpha$ ).

For more common conditions, such as thrombocytopenia, there will to 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,<sup>14</sup> 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).<sup>25</sup> 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	
	Source		Generic	Belgium specific
<b>1. Estimating background rates from hospital diagnosis reports</b>				
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	Challenges		Options for improvements	
	Source		Generic	Belgium specific
<b>2. Counting O by passive surveillance</b>				
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)	
<b>3. Counting exposed ones</b>				
	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
<b>4. Data analysis</b>				
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 AEFIs		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.<sup>39</sup> 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.<sup>40</sup> 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),

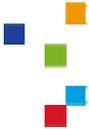
- Sensitivity (or ascertainment) of the data source: proportion of all nationally diagnosed cases that are captured by the system. This takes into account the coverage of the system and the level of under-reporting,
- Variables available (age, sex, specific subgroups),
- Other factors potentially influencing 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.<sup>1</sup> That this is an important issue, was illustrated for Belgium by a study of Aelvoet et al.,<sup>1</sup> 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 an 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 consist of around 200 GPs. This nationwide network represents approximately 1.8% of all Belgian GP's 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.<sup>41,42</sup> 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.<sup>43</sup> 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.<sup>2,3</sup> 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/epidemiology/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/ESC\\_AIDE2009\\_Session\\_19\\_Gergonne.pdf](http://ecdc.europa.eu/en/ESCAIDE/Materials/Presentations%202009/ESC_AIDE2009_Session_19_Gergonne.pdf). In Belgium, EuroMOMO monitoring is conducted by the IPH, which published a description of the Belgian MOMO system.<sup>44</sup>



### 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.<sup>4</sup> 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.<sup>4</sup> 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=rappports-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 Geïntegreerd 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, oculo-respiratory 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 oculo-respiratory 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)
<b>Autoimmune hepatitis</b>	2.53	1.11	2.68	1.83	0.52	1.00	3.77	2.07	11.79
<b>Anaphylaxis unspecified causes</b>	3.95	6.85	7.27	6.04	0.58	3.40	11.17	1.68	1.42
<b>Anaphylaxis known causes</b>	12.21	0.87	1.25	3.37	3.35	1.96	2.69	1.44	23.96
<b>Bells palsy</b>	33.14	31.68	10.90	16.56	25.59	5.07	29.10	48.03	7.00
<b>Convulsion</b>	72.81	249.63	179.19	301.74	156.70	110.06	377.62	42.74	107.90
<b>Demyelination</b>	16.39	15.88	51.71	18.45	6.09	6.98	39.79	8.90	15.54
<b>Encephalitis other causes</b>	22.72	4.26	5.07	2.78	0.42	2.27	2.77	1.82	2.29
<b>Encephalitis viral</b>	1.15	1.03		1.96	1.20	1.13	3.90	0.66	1.23
<b>Guillain-Barré Syndrome</b>	2.90	1.49	7.75	2.21	1.49	1.36	2.78	1.52	2.23
<b>Optical neuritis</b>	6.00	4.44	2.77	3.74	1.97	0.56		6.11	4.04
<b>Sudden death</b>	0.00		2.68	9.56		0.54	1.66		0.06
<b>Thrombocytopenia</b>	24.00	19.23	6.80	22.21	57.36	7.13	43.25	53.12	14.89
<b>Transverse myelitis</b>	0.02	0.92	0.26	0.77	0.41	0.22	0.93	0.71	
<b>Vasculitis</b>	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).

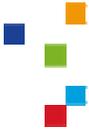
#### 5.1.1 Definitions

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.<sup>45</sup> 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”.<sup>46</sup> 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”.<sup>47</sup> 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).<sup>48</sup> 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.<sup>48</sup> 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.<sup>48</sup>

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.<sup>i</sup>

#### 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.<sup>49,50</sup>

An international review of SID summarized worldwide data over 1990-2005.<sup>50</sup> This review is mostly based on national statistics, no case definition is provided and the proportion of SID with autopsy is not described.<sup>50</sup> A number of 7 national studies describing SID rates in specific countries have been retrieved.<sup>49,51-56</sup> In addition, 5 studies assessing case definitions and the validity of SID coding have been retrieved.<sup>45,52,57-59</sup> 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.

<sup>i</sup> <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
<b>From national death statistics (death certificates)</b>					
Germany, 200550	National statistics, 1 week to 1 year	0.43	NA	NA	From <a href="http://www.gbe-bund.de">www.gbe-bund.de</a>
Ireland, 200550	National Death Register, birth to 1 year	0.38	NA	NA	From <a href="http://www.sidsireland.ie">www.sidsireland.ie</a>
Netherlands, 200550	National statistics, birth to <1 year	0.10	NA	NA	From <a href="http://www.cbs.nl">www.cbs.nl</a>
Norway, 200550	National statistics, birth to 1 year	0.30	NA	NA	From <a href="http://www.ssb.no">www.ssb.no</a>
Scotland, 200550	General register report, 1 week to 1 year	0.39	NA	NA	From <a href="http://www.statistics.gov.uk">www.statistics.gov.uk</a>
Sweden, 200550	National Statistics, birth to 1 year	0.23	NA	NA	From <a href="http://www.socialstyrelsen.se">www.socialstyrelsen.se</a>
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) <sup>56</sup>	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).
<b>From specific studies</b>					
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. <sup>59</sup> 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.

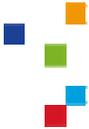


Table 6 and Figure 1 illustrate that studies based on (crude) national statistics, with no or limited validation of diagnosis, yield higher rates compared to those based on specific studies involving validation of diagnosis. Rates per 1000 live births vary across countries, with a range from 0.10 in 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.<sup>49,50,54,55</sup> 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.<sup>50</sup> Variations in rates are also seen within countries.<sup>49,50,55</sup> SID classically peaks during the 2<sup>nd</sup> to the 4<sup>th</sup> month of age and declines rapidly thereafter.<sup>47</sup> In a French prospective study of SID over 2007-09, two third of deaths occurred at home.<sup>49</sup>

#### 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.<sup>49</sup> 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).<sup>49</sup> 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%).<sup>54</sup>

#### 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.<sup>54</sup>

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.<sup>49</sup> 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.<sup>55</sup> Some studies suggested a diagnostic transfer between SID and unascertained deaths, as the numbers of unascertained deaths have risen considerably in some countries.<sup>52,55,57</sup> 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%.<sup>55</sup> 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%.<sup>52</sup> 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.<sup>56</sup>

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).<sup>54</sup> 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.<sup>53</sup>

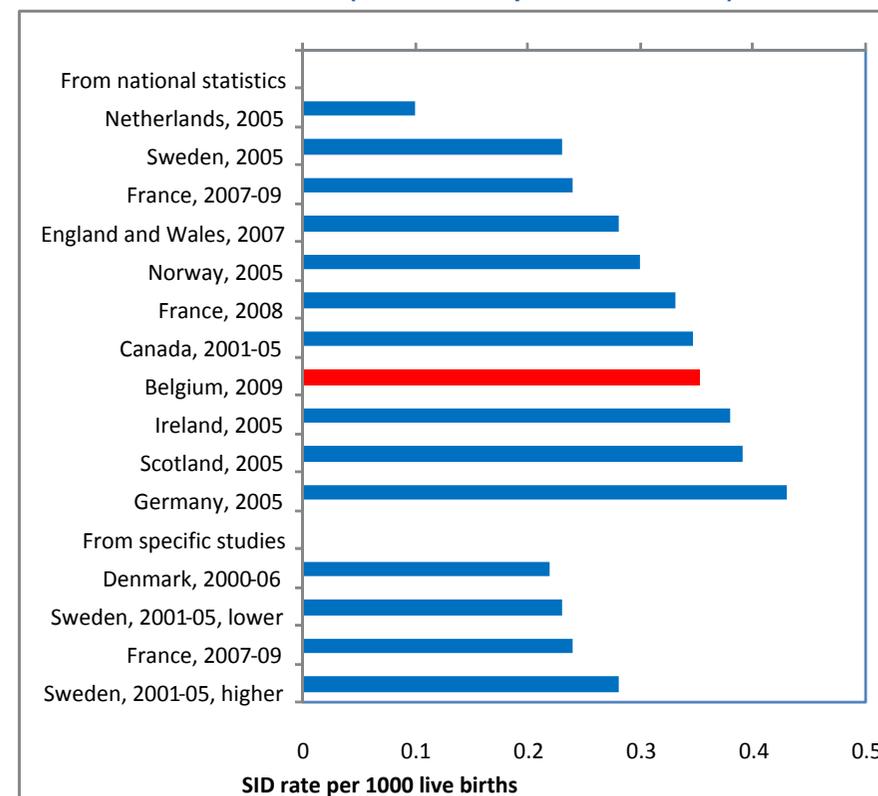


#### 5.1.2.4 Seasonal variations and temporal patterns

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.<sup>50</sup> 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.<sup>50,56</sup> 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.<sup>55</sup> 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.<sup>56</sup> 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.<sup>49</sup> In the Swedish study, no seasonality could be statistically detected.<sup>53</sup> 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.<sup>60</sup> 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.<sup>61</sup> 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.<sup>j</sup> A report from the French Community reported a high rate of SID in 1996 (1.08/1000 live births).<sup>62</sup> 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.<sup>63</sup>

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<sup>j</sup> <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.

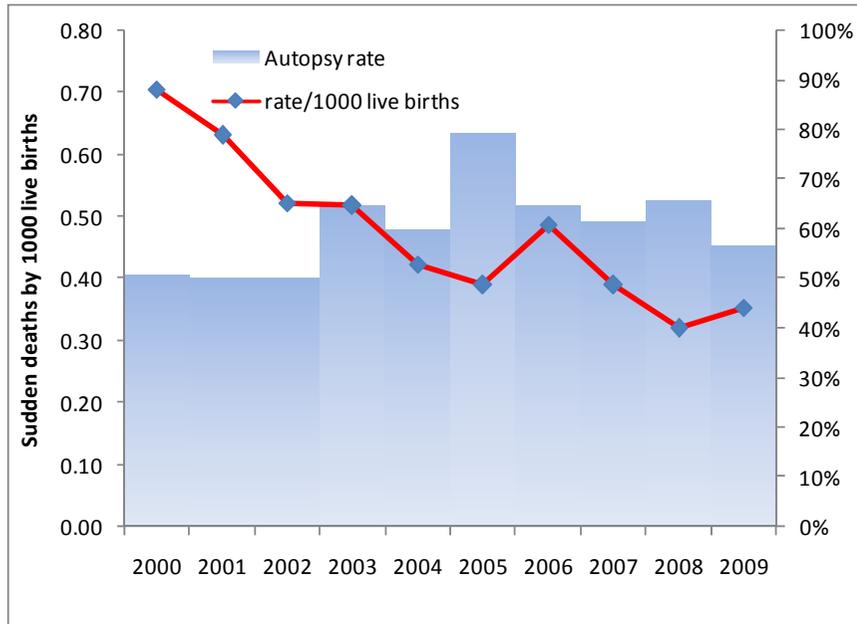
Among these deaths, around 60% had an autopsy ongoing or planned at the time of death coding. This proportion is similar across regions but increased slightly over the period, from a mean of 53% until the law was issued (2000-2003) to 65% hereafter (2004-09). Only few infant deaths were coded as “other 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.

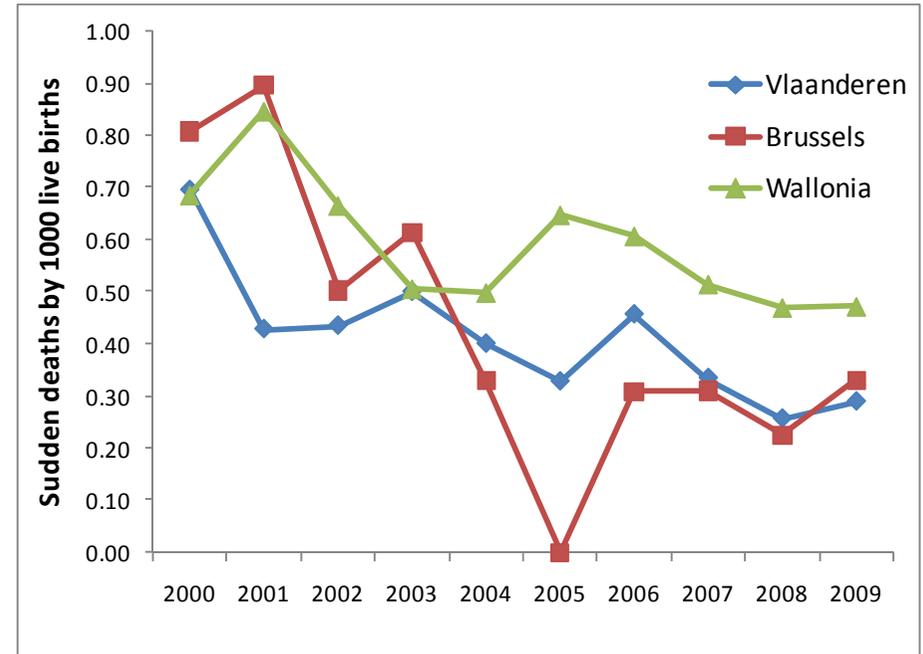


As illustrated in Figure 1, the recent rate in Belgium is comparable to those reported in other EU countries, and is closest to the rates from Canada, France and Ireland.

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

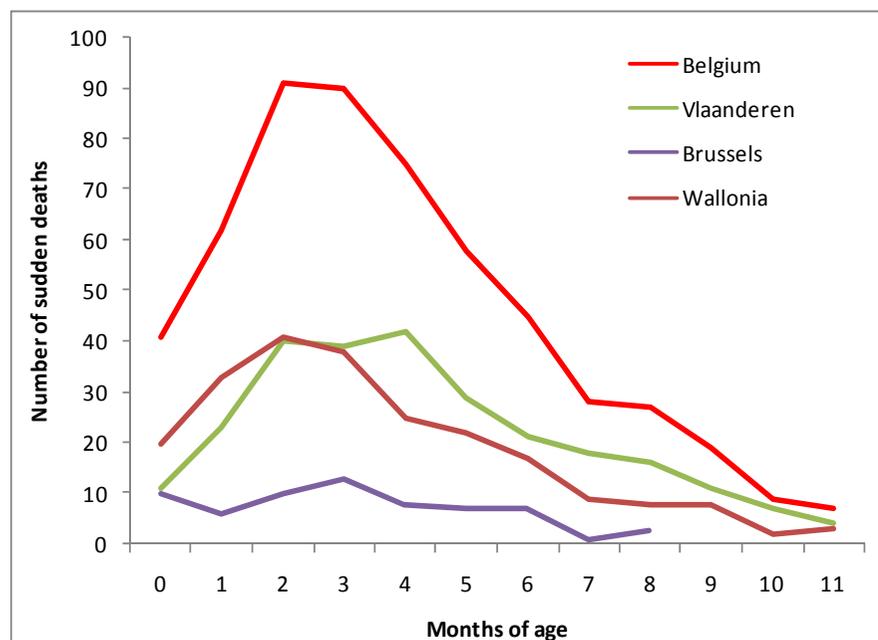


**Figure 3 – Sudden infant death rates in Belgium, by region, 2000-2009**





**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 $\geq 1$ 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.<sup>64</sup> 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.<sup>65-67</sup> 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).<sup>64</sup> 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.<sup>68</sup>



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.<sup>69</sup> 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.<sup>70</sup> The Brighton Collaboration has only defined unexplained sudden death in the first and second year of life.<sup>48</sup>

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

Concepts	Sources	Definitions
<b>Sudden death (SD)</b>	WHO ICD-10, 2012 (R96.1 and 96.2) <sup>64</sup> , Vaartjes, 2009 <sup>68</sup>	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.
	De la Grandmaison, 2006 <sup>65</sup> , Eckart, 2004 <sup>66</sup>	Natural, unexpected death within 1h of the onset of final symptoms (or inciting event)
<b>Sudden unexplained death</b>	Van der Werf, 2010 <sup>67</sup> Tan, 2005 <sup>69</sup> Eckart, 2011 <sup>71</sup>	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
<b>Sudden unexpected death</b>	Lim, 2010 <sup>70</sup>	SD in an apparently healthy subject or in one whose disease was not so severe that such an abrupt outcome could have been predicted
<b>Sudden cardiac death</b>	Eckart, 2011 <sup>71</sup>	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.<sup>68,72</sup>

### 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 ( $\geq 1$  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.<sup>68</sup> 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.<sup>k</sup> 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.<sup>65</sup> 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).<sup>68,73</sup> 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.<sup>68,74</sup> In addition, 13 other studies

described related information on definitions, coding and autopsy rates.<sup>65,67,69,70,72,75-82</sup> 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 $\geq 1$ year of age

Only one Dutch study estimated rates of sudden deaths from unknown causes in subjects aged 1-39 years of age.<sup>68</sup> 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.<sup>68</sup> 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.<sup>l</sup> In France (2008), the rate of deaths coded as R96, R98 and R99 accounted for 18.42/100 000 in all ages.<sup>74</sup>

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.<sup>72,75</sup>

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.<sup>76</sup> An US study on SCD found that 82% of cardiac arrests took place at home and 2% in community services.<sup>82</sup>

<sup>k</sup> <http://vaesco.net>

<sup>l</sup> [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](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 &gt;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 <sup>68</sup>	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 <sup>1</sup>	National death statistics in all ages	0.40 in all ages	14.2 in all ages		R99 ranked as 17 <sup>th</sup> 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 for 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%,<sup>76</sup> but was higher in the 1-19 years old compared to the 20-35 years old.<sup>75</sup> 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.<sup>82</sup>

### 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) (R96) were reported as main cause of death in Belgium, corresponding to an

an annual rate of 5.7/100 000 (Table 10). This rate varies widely across region, 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 ( $\leq 24$  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.<sup>82</sup> 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

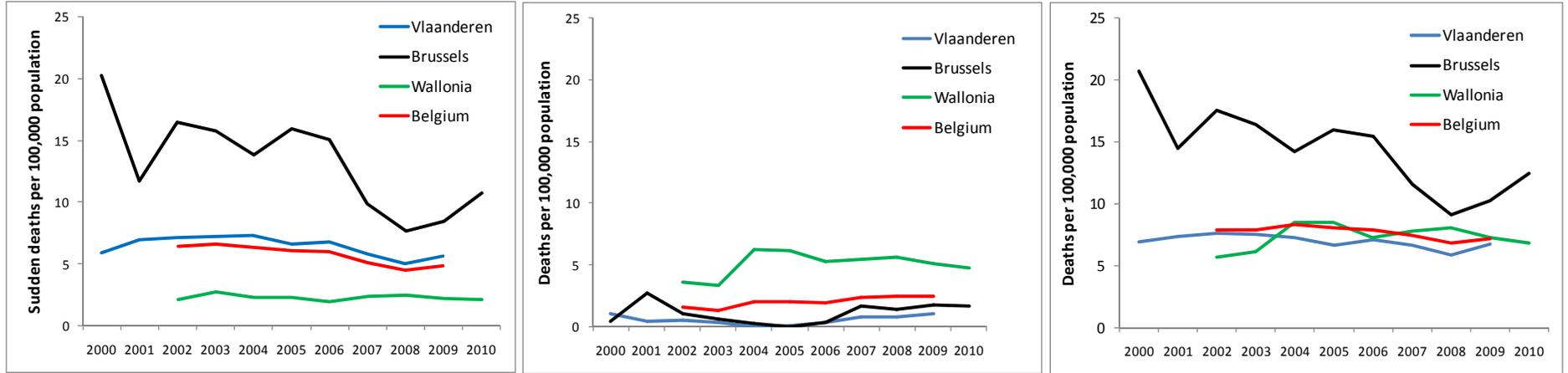
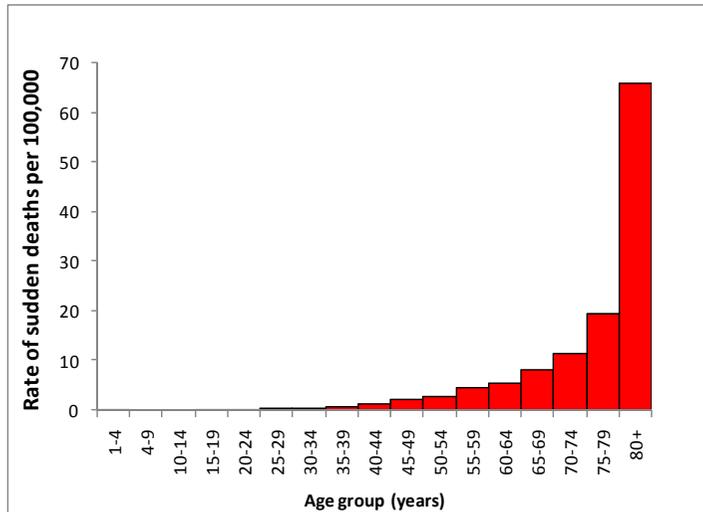
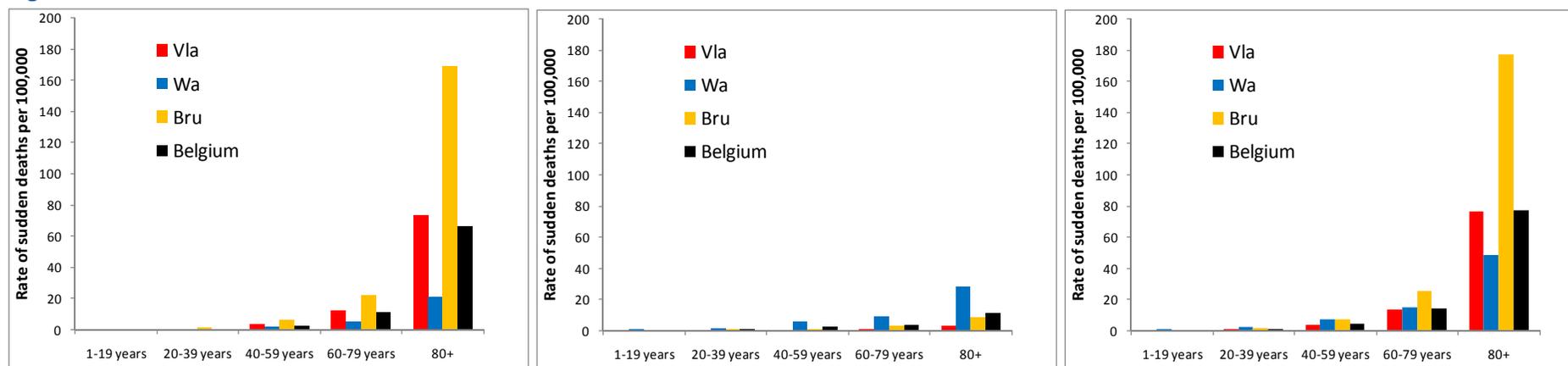


Figure 6 – Annual rate of sudden deaths (R96) by age group, Belgium, average 2002-09





**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  $\geq 80$  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  $\geq 60$  years of age and <0% in the  $\geq 80$  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.<sup>83</sup> Vaccines are another potential factor and associations between vaccines and GBS have been reported, although underlying mechanisms are not yet elucidated.<sup>83-86</sup> GBS is thus an important focus of vaccine safety monitoring and background incidence rates of GBS are important in signal detection.<sup>87,88</sup>

### 5.3.2 Definitions

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

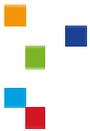
In 2009, the Brighton Collaboration GBS working group developed a standardized case definition for GBS and its variants to facilitate international comparison of GBS data in vaccine-vigilance.<sup>89</sup> This definition contains three levels of diagnostic certainty classification. However, most studies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

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.<sup>96</sup>

### 5.3.3 Literature review

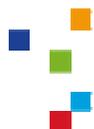
A literature review performed in 2009 for the KCE project Plasma, with search date up to December 2008, has been updated.

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.<sup>87,96</sup> 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.<sup>96</sup> Among the 10 selected studies estimating incidence in children ( $\leq 15$  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.<sup>87</sup> 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 <sup>88</sup>	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 <sup>97</sup>	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 <sup>91</sup>	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 <sup>94</sup>	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 <sup>93</sup>	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 <sup>98</sup>	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 <sup>92</sup>	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

<sup>a</sup> 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.<sup>88</sup> 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.<sup>87,96</sup> Some studies also showed that GBS declined with age after 70-80 years.<sup>93-95</sup> 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.<sup>87</sup>

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.<sup>24</sup> In Italy, Bogliun found a positive predictive value (PPV) of 54.8% of hospital discharge diagnosis, which was higher when databases were restricted to neurology wards.<sup>24</sup> 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.<sup>88</sup> 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.<sup>88,96</sup>

### 5.3.5 Seasonal or temporal patterns

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

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

### 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.<sup>93</sup> The thresholds were later recalculated by adding prospective data later collected.<sup>94</sup>

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.<sup>87</sup> 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**

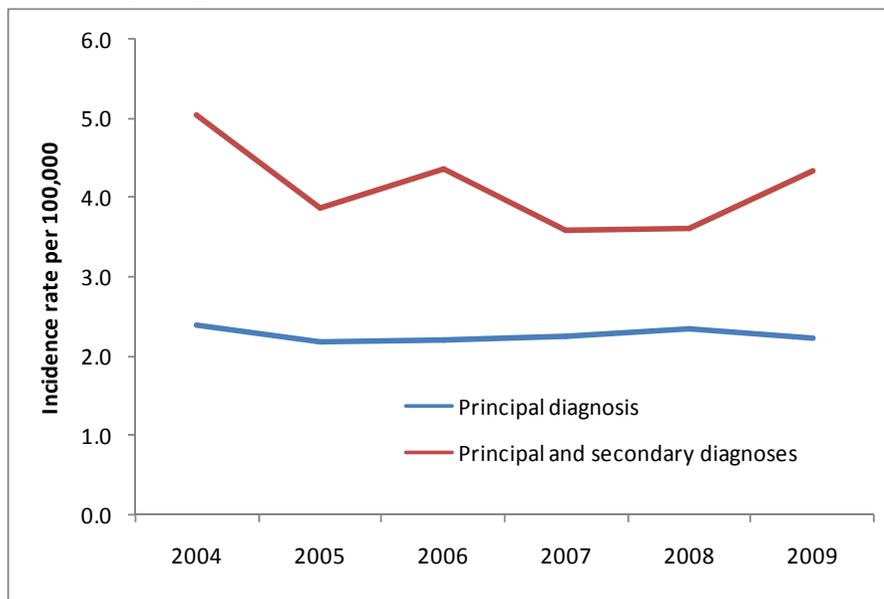


Table 12, based on principal and secondary diagnosis over 2000-07, shows that the mean hospitalization rate increases with increasing age. Corresponding annual hospitalization rates in children (0-18 years) ranged 1.0-2.2/100 000 and rates in adults (≥18 years) ranged 6.9-8.5/100 000 across the period.

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

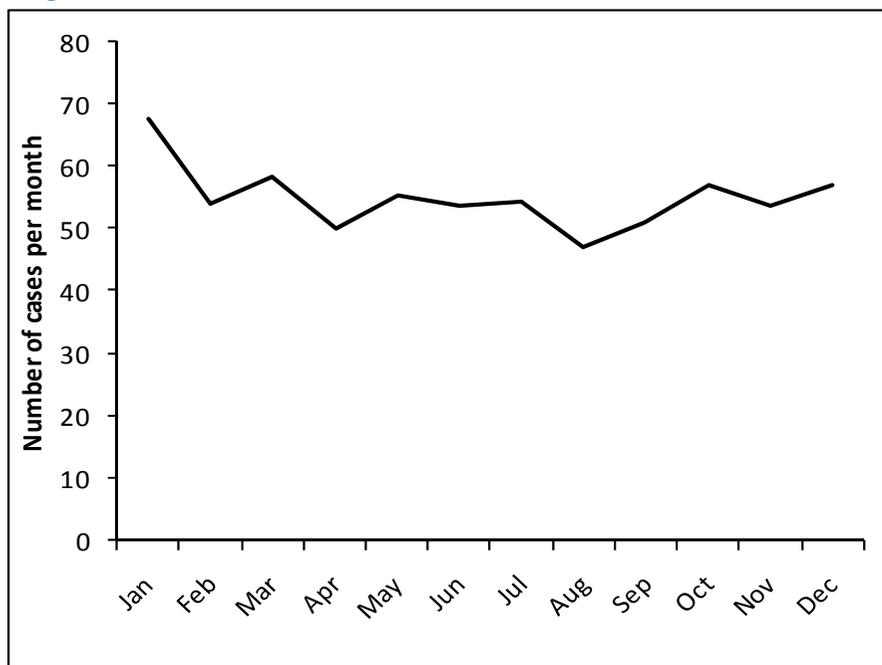
	N cases	Rates per 100 000
0-9 years	21	1.74
10-19 years	22	1.76
20-29 years	34	2.63
30-39 years	60	3.96
40-49 years	77	4.93
50-59 years	109	8.25
60-69 years	121	11.99
70-79 years	139	16.28
≥ 80 years	78	18.15
<b>Total</b>	<b>660</b>	<b>6.34</b>

*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.<sup>24,88,96</sup> 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.<sup>24</sup>

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.<sup>24</sup>
- 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 <sup>101</sup>	Patients with psychiatric disorders
Kelly et al, 2010 <sup>102</sup>	No incidence rates reported
Klein et al, 2010 <sup>103</sup>	Only relative risks reported
Miller et al, 2007 <sup>104</sup>	Only relative risks and risk per 10 000 doses reported
Stehr-Green et al, 2008 <sup>105</sup>	Only excess risk reported
Sun et al, 2012 <sup>106</sup>	Survival analysis, only Hazard rates reported
Svanström et al, 2010 <sup>107</sup>	No interpretable baseline incidence provided
Vahidnia et al, 2008 <sup>108</sup>	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.<sup>109</sup> 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.<sup>110</sup> 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.<sup>111</sup> 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.<sup>112</sup> 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%.<sup>113</sup>

Hamdy et al.<sup>114</sup> 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.<sup>115,116</sup> 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.<sup>117</sup> 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 <sup>111</sup>	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 <sup>109</sup>	Prospective cohort study	71.3/100 000 population per year	Acute symptomatic seizures and unprovoked seizures	Afebrile
US <sup>109</sup>	Retrospective cohort	100.0/100 000 population per year	Acute symptomatic seizures and unprovoked seizures	Afebrile
Sweden <sup>109</sup>	Prospective cohort study	76.0/100 000 population per year	Acute symptomatic seizures and unprovoked seizures	Afebrile
Switzerland <sup>109</sup>	Prospective cohort study	70.8/100 000 population per year	Acute symptomatic seizures and unprovoked seizures	Afebrile
Denmark <sup>112</sup>	Register based	Cumulative incidence at age 5 3.9% Peak between 10 and 20 months	Febrile seizures	No yearly incidences given
Australia <sup>110</sup>	Register based	248/100 000 population per year (all ages)	All seizure	Only seizures presenting at emergency departments.
UK <sup>114</sup>	Register based, pediatric services UK	284/100 000 population per year at age 5	All seizure	Bradford, large ethnic discrepancies found
Finland <sup>115,116</sup>	Prospective cohort study	Cumulative incidence at age 5 6.9% Peak between 10 and 20 months	Febrile seizure	Lower in retrospective cohort
UK <sup>118,119</sup>	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 convulsion 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 convulsion 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
<b>ATC CODE : J06BA01 - Immunoglobulins, normal human, for extravascular administration</b>		
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
<b>ATC CODE : J06BA02 - Immunoglobulins, normal human, for intravascular administration</b>		
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 immunoglobulin'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,

Purpura thrombocytopenique 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.

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.

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 + elctromyogramme + 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 demyelating disease, Guillain-Barré syndrome, Optic neuritis and Bell's palsy, we used the unique patient identifier to try to weed 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 weed 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
<b>TOTAL</b>	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
<b>TOTAL</b>	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
<b>TOTAL</b>	<b>72857</b>		

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
<b>2004</b>	809	7.9	12.3	739	128.0	164	278	273	469
<b>2005</b>	867	8.4	13.2	788	136.9	165	283	292	492
<b>2006</b>	924	8.9	14.0	728	127.1	133	231	276	471
<b>2007</b>	942	9.1	14.5	862	150.9	180	311	290	501
<b>2008</b>	1020	9.8	15.6	944	164.2	307	510	327	560
<b>2009</b>	890	8.5	13.5	807	139.0	207	337	297	489
<b>TOTAL</b>	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 demyelating 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
<b>TOTAL</b>	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
<b>TOTAL</b>	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
<b>2004</b>	24	329	25	378	3.68	3.09
<b>2005</b>	15	300	25	340	3.41	2.88
<b>2006</b>	13	290	20	323	3.19	2.73
<b>2007</b>	8	320	18	346	3.42	2.87
<b>2008</b>	9	280	21	310	3.05	2.57
<b>2009</b>	11	309	17	337	3.34	2.87
<b>TOTAL</b>	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
<b>2004</b>	12280		119.6	85.6
<b>2005</b>	12891		125.0	89.6
<b>2006</b>	10497		101.4	71.5
<b>2007</b>	13743		132.2	94.4
<b>2008</b>	13569		129.9	93.4
<b>2009</b>	11982		114.0	79.0
<b>TOTAL</b>	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%
<b>Total</b>	<b>1031</b>	<b>100.00%</b>

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/geneesmiddelenbewaking/info\\_icsrs\\_-\\_mah\\_sponsors/](http://www.fagg-afmps.be/nl/MENSELIJK_gebruik/geneesmiddelen/geneesmiddelen/geneesmiddelenbewaking/info_icsrs_-_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)<sup>m</sup> 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.

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<sup>m</sup> 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:

$$\chi = \sqrt[3]{9\tilde{O}} * (1 - \frac{1}{9\tilde{O}} - \sqrt[3]{\frac{E}{\tilde{O}}})$$

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

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

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

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

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 variable<sup>13</sup>**

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 patients 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.,<sup>1</sup> 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 alphanumeric, 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.<sup>120</sup>

#### 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-CM<sup>n</sup> 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.

<sup>n</sup> 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 Integoo 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 Integoo 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 Integoo database is currently 1.95% of the Flemish population.

### Representativeness of the source population

The patient population in the Integoo 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.

<sup>o</sup> <http://www.integoo.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 (rijksregisternummer/numéro de registre 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

## Appendix 2.7. Pedisurv

### Data providers

In 2002 the network PediSurv (**P**ediatric diseases **S**urveillance) 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 paediatricians 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 Geïntegreerd 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 reports 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 heath 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/psychology[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:

Gammanorm, Hizentra, Subcuvia, Vivaglobin

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<sub>2</sub>- ofwel het IgG<sub>3</sub>-gehalte, als volgt verlaagd zijn:

- volwassenen: IgG-gehalte < 7,50 g/l; IgG<sub>2</sub>-gehalte < 1,50 g/l; IgG<sub>3</sub>-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<sub>2</sub>/IgG<sub>3</sub>-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 hypogammaglobulinemie en recidiverende infecties.

Op grond van een omstandig verslag dat is opgemaakt door een geneesheer-specialist 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

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<sub>2</sub> ou IgG<sub>3</sub> est la suivante:

- adultes : taux d'IgG < 7,50 g/l ; taux d'IgG<sub>2</sub> < 1,50 g/l ; taux d'IgG<sub>3</sub> < 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<sub>2</sub>/IgG<sub>3</sub> 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



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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)

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

### Chapter IV

§ 90 000

#### Immunoglobulins:

#### Gammagard

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 recidive-rende infecties zijn opgetreden waarvoor herhaaldelijk antibiotica-therapie noodzakelijk was. Deze deficiëntie moet gedocumenteerd zijn door het falen van de anti-lichaam-productie na pneumococcenvaccinatie.

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

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

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<sub>2</sub> ou IgG<sub>3</sub> est la suivante:

- adultes : taux d'IgG < 7,50 g/l ; taux d'IgG<sub>2</sub> < 1,50 g/l ; taux d'IgG<sub>3</sub> < 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<sub>2</sub>/IgG<sub>3</sub> 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.



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.

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 verantwoording voor de behandeling moet de bewijsstukken waaruit blijkt dat aan alle voornoemde voorwaarden wordt voldaan, desgevraagd kunnen bezorgen aan de adviserend geneesheer van de verzekeringsinstelling.

4. Purpura thrombocytopenique 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.

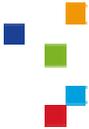
6. Maladie de Kawasaki.

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.



## 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 IgG<sub>2</sub>- ofwel het IgG<sub>3</sub>-gehalte, als volgt verlaagd zijn:

- volwassenen: IgG-gehalte < 7,50 g/l; IgG<sub>2</sub>-gehalte < 1,50 g/l; IgG<sub>3</sub>-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<sub>2</sub>/IgG<sub>3</sub>-deficiëntie te wijten is aan een chronische behandeling met corticosteroiden 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 hypogammaglobulinemie en recidiverende infecties.

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

## 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 IgG<sub>2</sub> ou IgG<sub>3</sub> est la suivante:

- adultes : taux d'IgG < 7,50 g/l ; taux d'IgG<sub>2</sub> < 1,50 g/l ; taux d'IgG<sub>3</sub> < 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<sub>2</sub>/IgG<sub>3</sub> 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 prematuren en in de neonatale periode.

10. Ter behandeling van ernstige multifocale motor neuropathie (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 aantoonst en dit buiten de gebruikelijke compressie zones (de cubitale zenuw in de elleboog, de heupknieholte 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 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 concernerait plusieurs muscles.

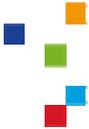
Le remboursement est accordé pour autant que :

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 gevolgd door onderhoudskuren waarbij de frekwentie en de dosis bepaald worden door de klinische tekens van herstel 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-psiatrie, 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 Demyelating 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 of tricyclische derivaten).

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

voor 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 récurrence 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 Demyelating Polyneuropathy ou CIPD) 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 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 geleidingsnelheid 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 spieractiepotaal) motor 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/mm<sup>3</sup> in het geval van een negatieve HIV-serologie of lager dan 50/mm<sup>3</sup> 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 herhal 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-psiatrie, 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 poplitée externe à la tête du péroné).

5°) Cellulorachie inférieure à 15 globules blancs/mm<sup>3</sup> si la sérologie VIH est négative ou inférieure à 50/mm<sup>3</sup>, 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'entière des anomalies cliniques et/ou neurophysiologiques.

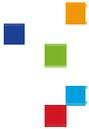
Pendant une première période de six mois, le nombre de conditionnements remboursables tiendra compte d'une quantité totale maximum de 9,0 g/kg, pour l'ensemble des cures de cette période.

La cure initiale sera suivie si nécessaire de cures d'entretien dont la fréquence et la dose dépendent des signes cliniques de récidence 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 IgG<sub>2</sub>- ofwel het IgG<sub>3</sub>-gehalte, als volgt verlaagd zijn:

- volwassenen: IgG-gehalte < 7,50 g/l; IgG<sub>2</sub>-gehalte < 1,50 g/l; IgG<sub>3</sub>-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<sub>2</sub>/IgG<sub>3</sub>-deficiëntie te wijten is aan een chronische behandeling met corticosteroiden 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 antilichaamproductie na pneumococcenvaccinatie.

2. Myeloom en CLL met ernstige secundaire hypogammaglobulinemie 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 IgG<sub>2</sub> ou IgG<sub>3</sub> est la suivante :

- adultes : taux d'IgG < 7,50 g/l ; taux d'IgG<sub>2</sub> < 1,50 g/l ; taux d'IgG<sub>3</sub> < 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<sub>2</sub>/IgG<sub>3</sub> 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 aantoonst en dit buiten de gebruikelijke compressie zones (de cubitale zenuw in de elleboog, de heupknieholte 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 thrombocytopenique 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 concernerait 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 herstel 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-psiatrie, 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 Demyelating 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 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 récurrence 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 Demyelating Polyneuropathy ou CIPD) 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 sensoriele 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 spieractiepotaal) motor 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/mm<sup>3</sup> in het geval van een negatieve HIV-serologie of lager dan 50/mm<sup>3</sup> 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 herstel 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-psiatrie, 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).

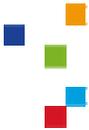
5°) Cellulorachie inférieure à 15 globules blancs/mm<sup>3</sup> si la sérologie VIH est négative ou inférieure à 50/mm<sup>3</sup>, si la sérologie VIH est positive.

6°) Exclusion formelle, via une anamnèse et un examen clinique réalisés de façon exhaustive, de toute autre neuropathie démyélinisante pouvant rendre compte de l'entière 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 récurrence 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 cellulorachie 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:

Kiovig, Nanogam, Octagam, Privigen

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<sub>2</sub>- ofwel het IgG<sub>3</sub>-gehalte, als volgt verlaagd zijn:

- volwassenen: IgG-gehalte < 7,50 g/l; IgG<sub>2</sub>-gehalte < 1,50 g/l; IgG<sub>3</sub>-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<sub>2</sub>/IgG<sub>3</sub>-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 hypogammaglobulinemie en

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<sub>2</sub> ou IgG<sub>3</sub> est la suivante :

- adultes : taux d'IgG < 7,50 g/l ; taux d'IgG<sub>2</sub> < 1,50 g/l ; taux d'IgG<sub>3</sub> < 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<sub>2</sub>/IgG<sub>3</sub> 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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