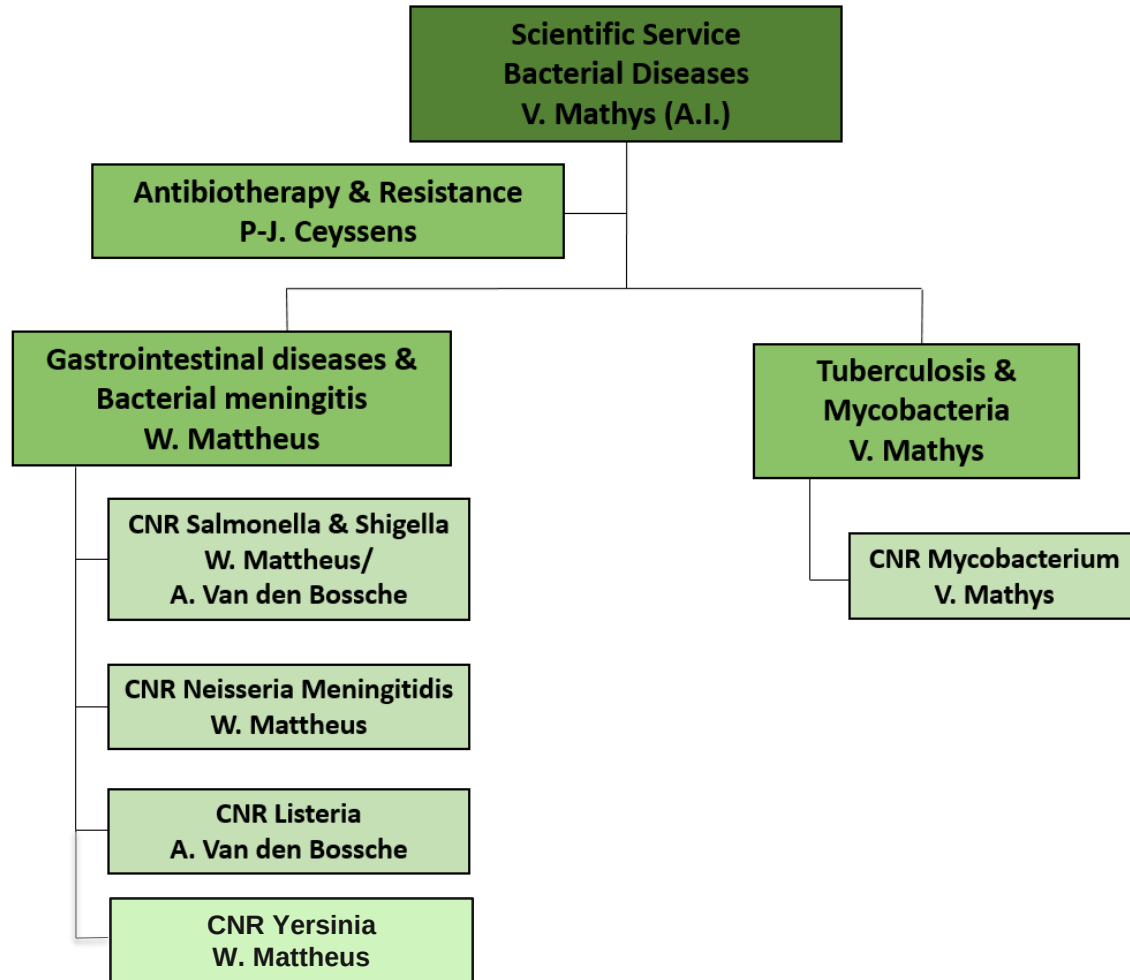


MENINGOKOKKENZIEKTE? ANNO 2020

Wesley Mattheus

NRC Neisseria bij Sciensano



NRC *Neisseria meningitidis*

➤ Rol

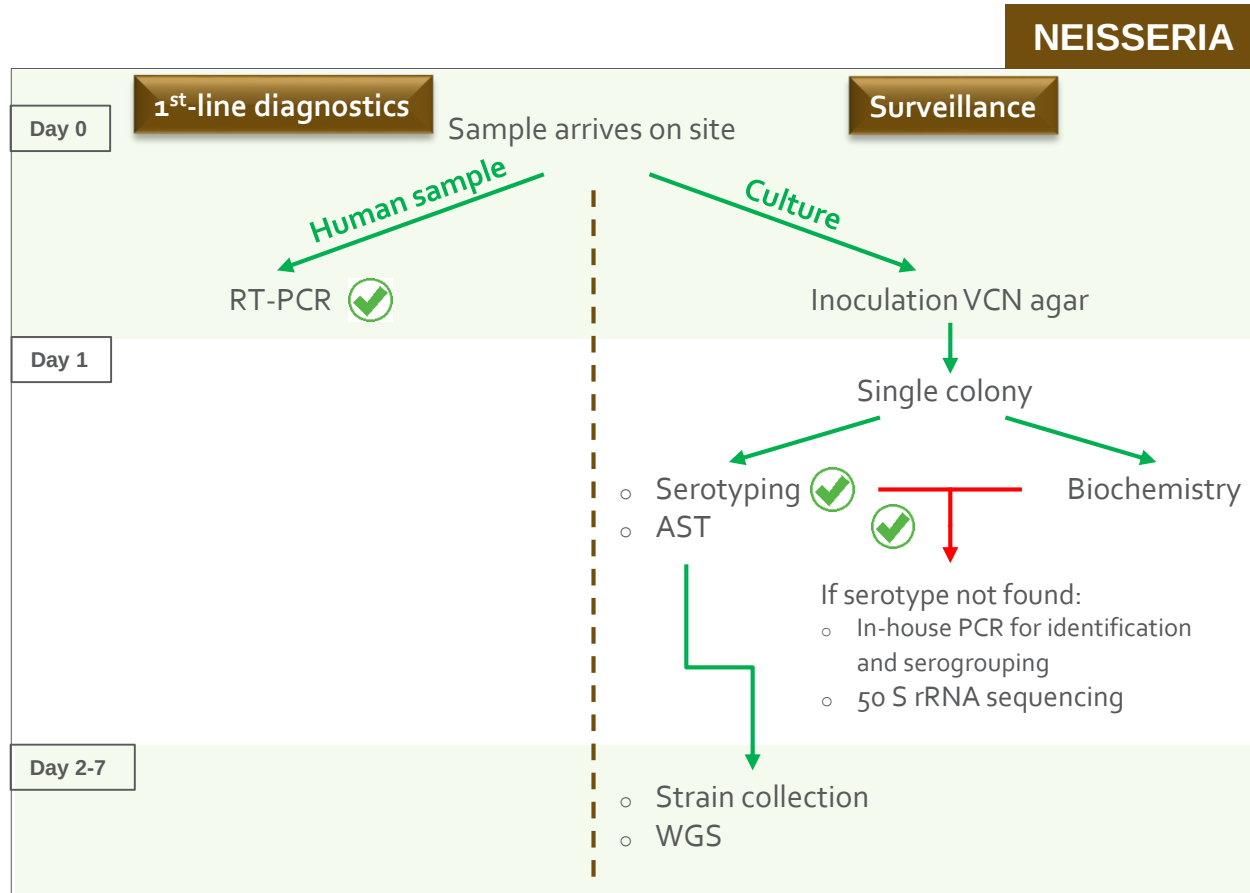
- Bevestigen van de diagnose van het primaire labo, serogroep determinatie en antibiotica resistentie profiel
 - Impact op profylactische antibiotica behandeling en vaccinatie van directe omgeving
- Snelle moleculaire diagnostische testen voor niet-kweekbare stalen
 - Voor de meest voorkomende bacteriële meningitis-veroorzakende pathogenen (*Neisseria meningitidis*, *Listeria monocytogenes*, *Streptococcus pneumoniae*, *Haemophilus influenzae*)
- Moleculaire subtypering van stammen
 - Vroege cluster detectie en epidemiologische surveillance

➤ ISO15189 accreditatie (9 testen)

- Biochemische identificatie van *N. meningitidis*
- Serogroep determinatie *N. meningitidis* door agglutinatie
- Antibiotica resistentie *N. meningitidis*
- MLST *N. meningitidis*
- PorA/FetA typeren *N. meningitidis*
- Detectie *N. meningitidis* door Real time PCR
- Detectie *S. pneumoniae* door Real time PCR
- Detectie *H. influenzae* door Real time PCR
- Serogroep determinatie *N. meningitidis* door Real time PCR

NRC Neisseria meningitidis

Workflow



WGS basen verbeterde IMD surveillance

Neisseria Pipeline

Klassieke moleculaire typering:

- PorA
- FetA
- 7-genes MLST

Publications: Validation of a bioinformatics workflow for routine analysis of whole genome sequencing data and related challenges for pathogen typing in a European National Reference Center: *Neisseria meningitidis* as a proof-of-concept. Bogaerts et al., *Frontiers in Microbiology*, 2019.

Sequence typing

Classic MLST

ST	clonal complex
6765	ST-213 complex

Locus	Allele	% Identity	HSP/locus length	Type	Alignment
abcZ	329	100.00	433/433	DNA	view
adk	5	100.00	465/465	DNA	view
aroE	1	100.00	490/490	DNA	view
fumC	13	100.00	465/465	DNA	view
gdh	36	100.00	501/501	DNA	view
pdhC	53	100.00	480/480	DNA	view
pgm	15	100.00	450/450	DNA	view

[Download \(TSV\)](#)
Last updated: 14-01-2019

PorA variable regions

Locus	Allele	% Identity	HSP/locus length	Type	Alignment
PorA_VR1	1-22	100.00	18/18	peptide	view
PorA_VR2	2-14	100.00	10/10	peptide	view

[Download \(TSV\)](#)
Last updated: 14-01-2019

FetA

Locus	Allele	% Identity	HSP/locus length	Type	Alignment
FetA	F5-5	100.00	42/42	peptide	view

[Download \(TSV\)](#)
Last updated: 14-01-2019

Internationale nomenclatuur
beschikbaar op PubMLST

WGS basen verbeterde IMD surveillance

Neisseria Pipeline

Verbeterde moleculaire typering:

- cgMLST – **1605 genen**
- High resolution clustering
- Nationale database bij NRC
- Internationale database

IMD Belgium 2019

Galaxy

Tools

search tools

Get Data
Send Data
Lift-Over
Text Manipulation
Filter and Sort
Join, Subtract and Group
Convert Formats
Extract Features
Fetch Sequences
Fetch Alignments
NGS: Variant Analysis
NGS: SNP Phylogeny
NGS: QC and manipulation
NGS: Read mapping
NGS: Assembly
NGS: Pipelines
NGS: GATK Tools
NGS: Picard
NGS: Taxonomic classification
NGS: Decontamination

Analyze Data

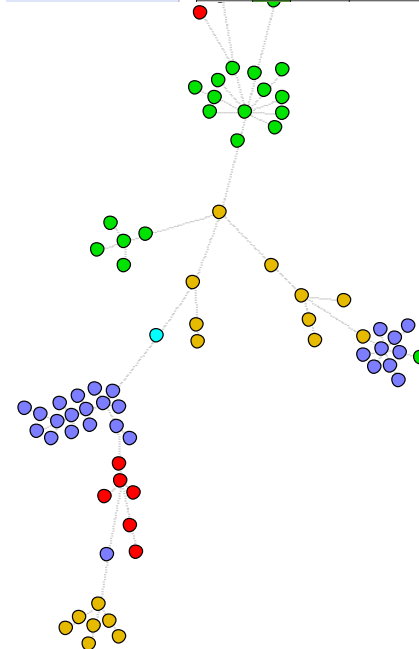
Worlds

cgMLST

Show / hide alleles

☒

Locus	Allele	% Identity	HSP/locus length	Type	Alignment
NEIS0001	24	100.00	924/924	DNA	view
NEIS0004	5	100.00	330/330	DNA	view
NEIS0005	52	100.00	198/198	DNA	view
NEIS0006	44	100.00	954/954	DNA	view
NEIS0007	149	100.00	2058/2058	DNA	view
NEIS0008	467	100.00	1839/1839	DNA	view
NEIS0009	15	100.00	519/519	DNA	view
NEIS0010	343	100.00	1326/1326	DNA	view
NEIS0011	241	100.00	840/840	DNA	view
NEIS0012	64	100.00	1167/1167	DNA	view
NEIS0013	88	100.00	1266/1266	DNA	view
NEIS0014	45	100.00	330/330	DNA	view



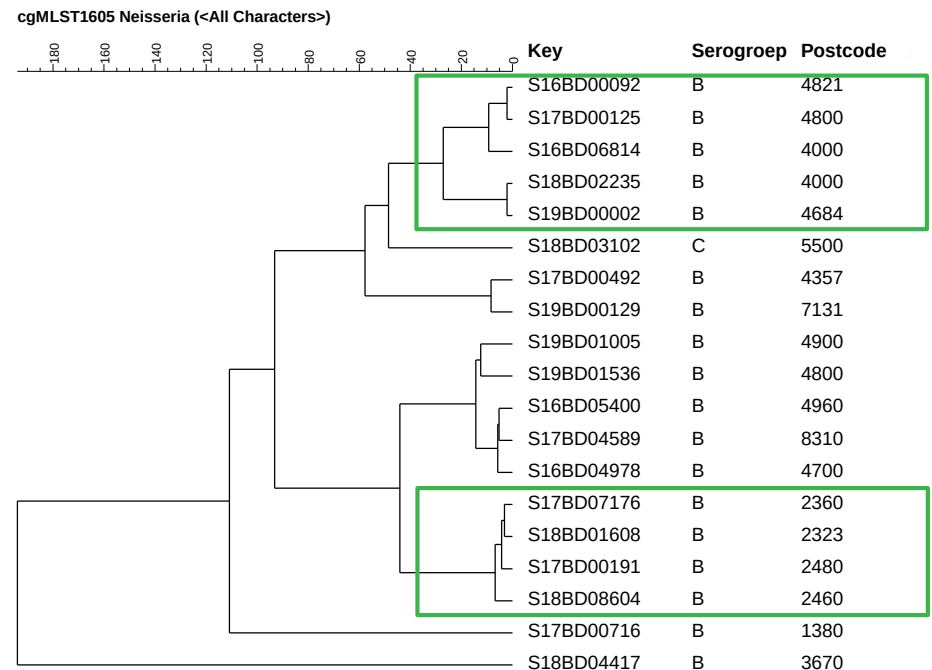
WGS basen verbeterde IMD surveillance

Verbeterde moleculaire surveillance

‘Real time’ High resolution clustering

Voorbeeld:

- MenB cluster Liège 2018-2019
- MenB cluster Antwerp 2017-2018



Epidemiologie en Vaccin strategie

Beschikbare vaccins:

Geconjugeerde polysacharide vaccins:

- Goede immuunrespons (T-cel) in baby's
- Bewezen groepsimmunititeit
 - MenC: Neisvac-C, Menjugate
 - MenACWY: Nimenrix (>6weken), Menveo (>2jaar)

Recombinante proteïnen vaccins - MenB:

- Geen bewezen groepsimmunititeit
 - Bexsero (4CMenB): >6weken (2+1)
 - Trumenba: >10jaar (1+1 or 2+1)

Epidemiologie en Vaccin strategie

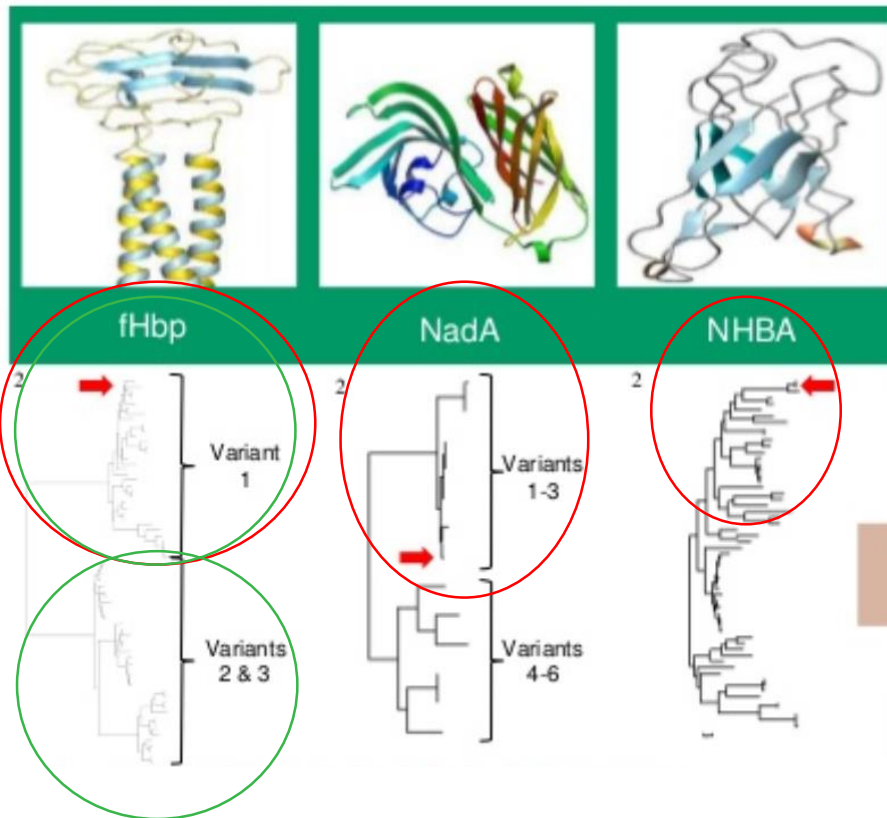
MenB vaccins

Vaccin doelwitten:

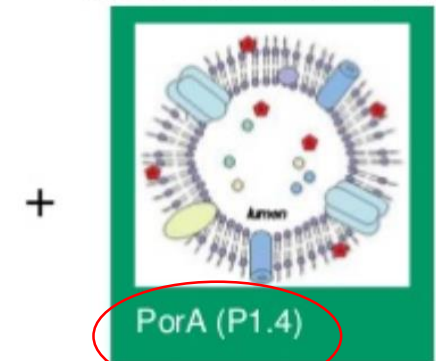
MenB vaccin
« Bexsero »

MenB vaccin
« Trumenba »

Three recombinant proteins discovered by reverse vaccinology.



OMVs from the New Zealand outbreak strain (NZ 98/254).



249 VR1 variants³
649 VR2 variants⁴

Expression of proteins
is variable

¹<http://www.inpharm.com/news/101223/novartis-meningococcal-vaccine-bexsero>

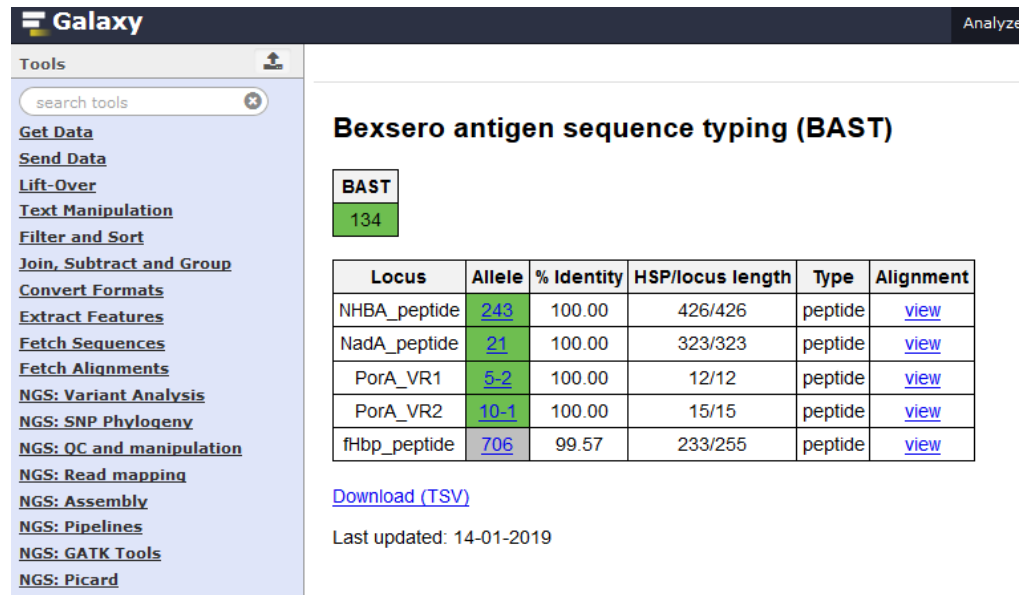
²Vogel U et al, Lancet Infect Dis 2013;13:416-25.

Epidemiologie en Vaccin strategie

Verbeterde moleculaire surveillance

Vaccin doelwitten:

MenB vaccin
« Bexsero »



The screenshot shows the Galaxy web interface. On the left is a sidebar with a 'Tools' section containing a search bar and a list of tool categories: Get Data, Send Data, Lift-Over, Text Manipulation, Filter and Sort, Join, Subtract and Group, Convert Formats, Extract Features, Fetch Sequences, Fetch Alignments, NGS: Variant Analysis, NGS: SNP Phylogeny, NGS: QC and manipulation, NGS: Read mapping, NGS: Assembly, NGS: Pipelines, NGS: GATK Tools, and NGS: Picard. The main panel displays the 'Bexsero antigen sequence typing (BAST)' tool results. It includes a small table with 'BAST' and '134'. Below this is a larger table with columns: Locus, Allele, % Identity, HSP/locus length, Type, and Alignment. The table lists five entries: NHBA_peptide (Allele 243, 100.00% identity, 426/426 length), NadA_peptide (Allele 21, 100.00% identity, 323/323 length), PorA_VR1 (Allele 5-2, 100.00% identity, 12/12 length), PorA_VR2 (Allele 10-1, 100.00% identity, 15/15 length), and fHbp_peptide (Allele 706, 99.57% identity, 233/255 length). Each entry has a 'view' link in the Alignment column. Below the table is a 'Download (TSV)' link and the text 'Last updated: 14-01-2019'.

Locus	Allele	% Identity	HSP/locus length	Type	Alignment
NHBA_peptide	243	100.00	426/426	peptide	view
NadA_peptide	21	100.00	323/323	peptide	view
PorA_VR1	5-2	100.00	12/12	peptide	view
PorA_VR2	10-1	100.00	15/15	peptide	view
fHbp_peptide	706	99.57	233/255	peptide	view

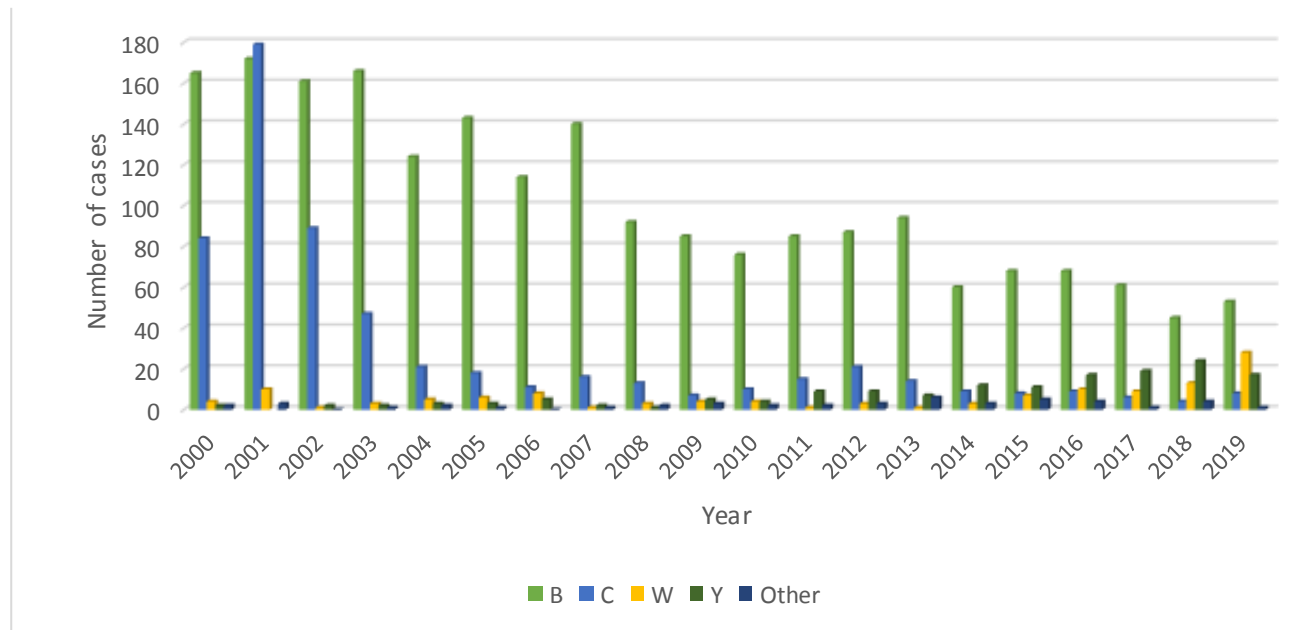
[Download \(TSV\)](#)
Last updated: 14-01-2019

Bexsero biedt bescherming tegen ongeveer 85% van de stammen

Epidemiologie en Vaccin strategie

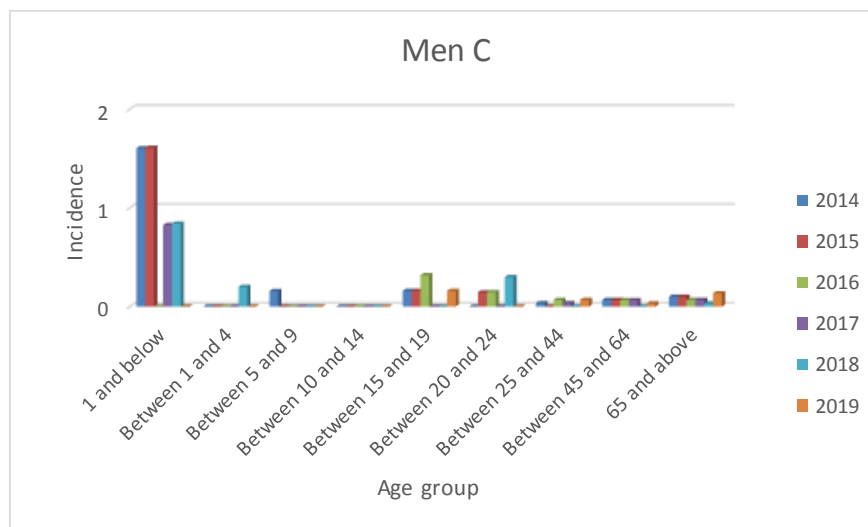
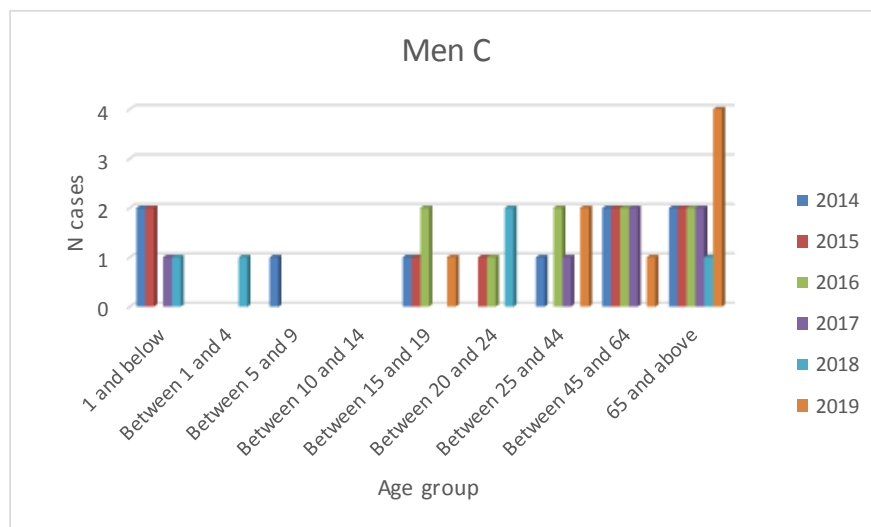
IMD in België – Per serogroep

↓ Introductie MenC vaccinatie



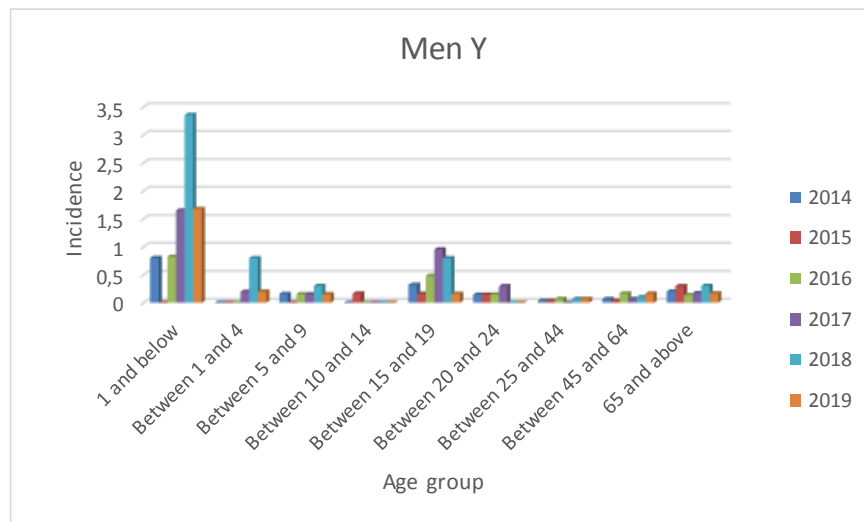
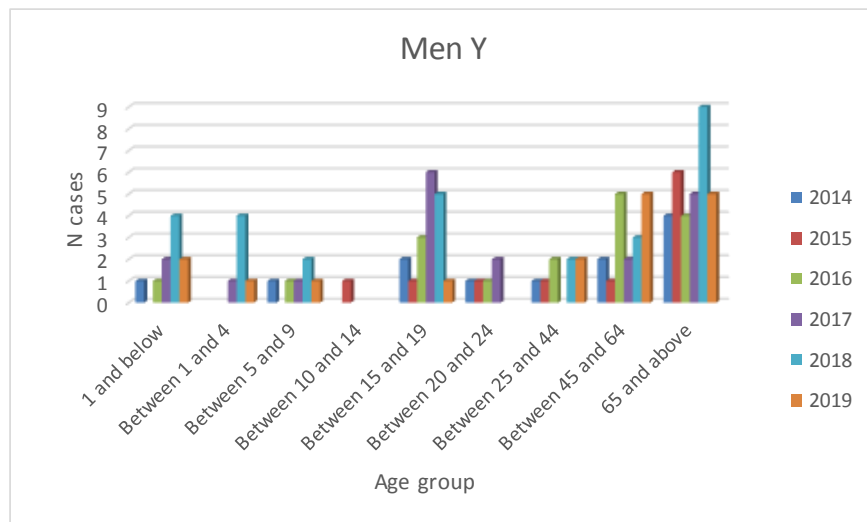
Epidemiologie en Vaccin strategie

MenACWY IMD in België – Per leeftijdsgroep



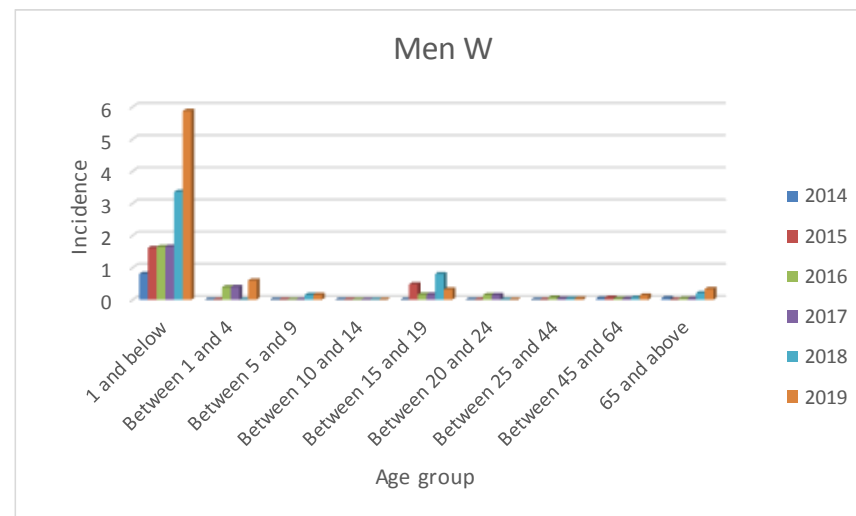
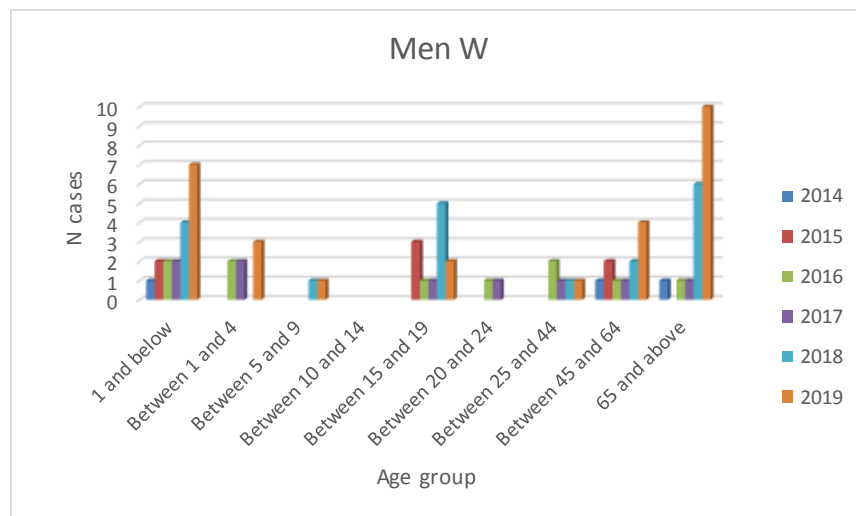
Epidemiologie en Vaccin strategie

MenACWY IMD in België – Per leeftijdsgroep



Epidemiologie en Vaccin strategie

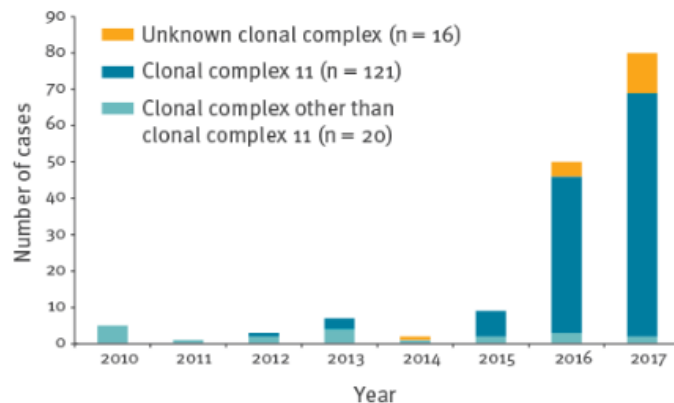
MenACWY IMD in België – Per leeftijdsgroep



Epidemiologie en Vaccin strategie

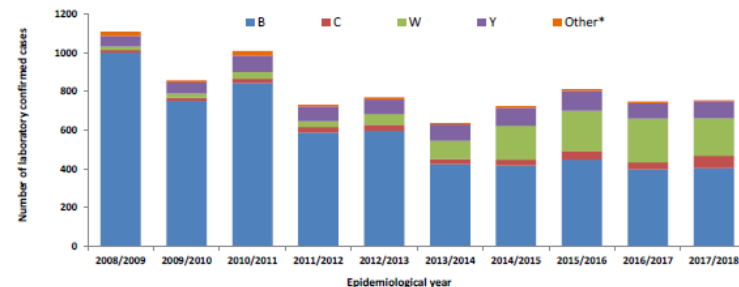
Internationale toename van MenW

MenW Nederland



MenW UK

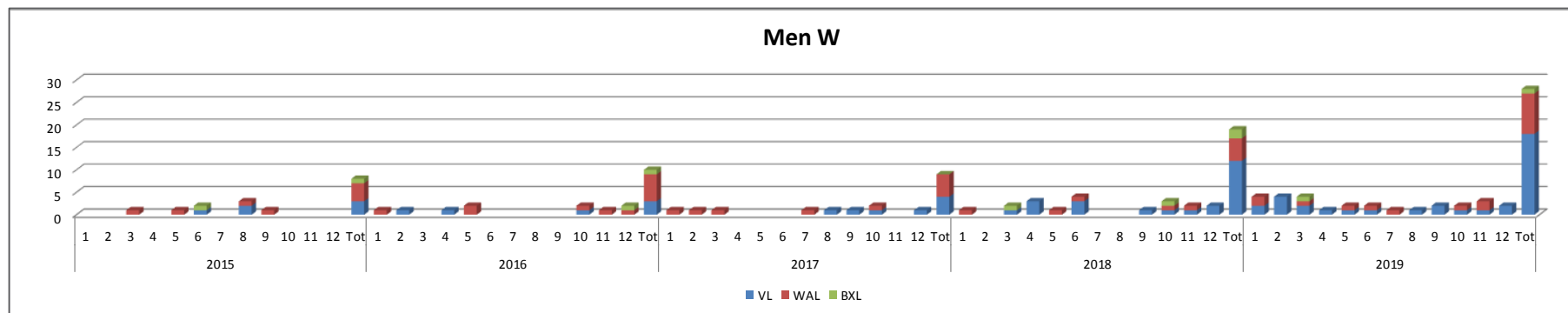
Figure 1. Invasive meningococcal disease in England by capsular group: 2008/2009 to 2017/2018



- Endemisch hypervirulente stammen
- Cc-11
- Atypische klinische manifestatie en fatale gevallen

Epidemiologie en Vaccin strategie

Toename van MenW in België



- Toename in hele land
- 2019:
 - 28 gevallen van MenW
 - 4 letale gevallen, 3 jonge kinderen

Epidemiologie en Vaccin strategie

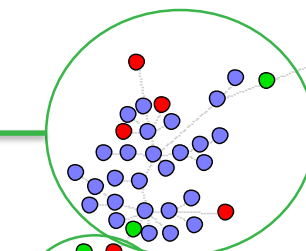
Toename van MenW in België

Duidelijke regionale verschillen:

- Epidemische cc11-strain voornamelijk in Vlaanderen
- ST-9316 clone in Wallonië
 - Ook geobserveerd in het Noorden van Frankrijk

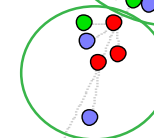
'Real time' High resolution clustering

UK-2013/NL 2018

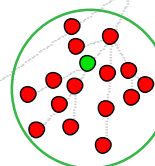


■ Bxl
■ Wal
■ VL

Hajj - 2001

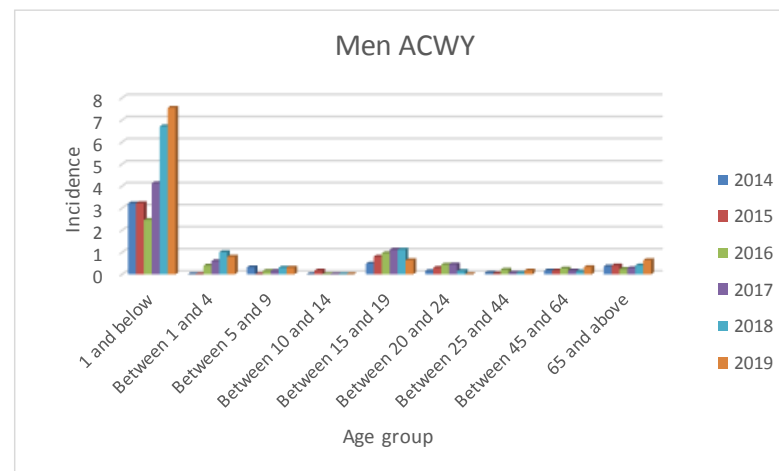
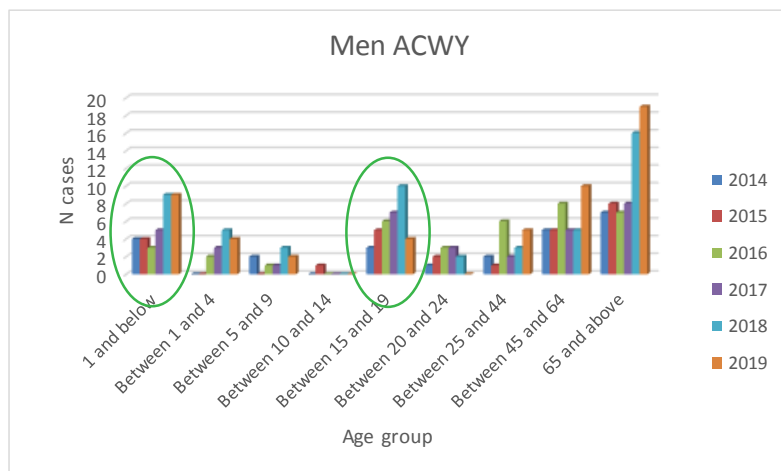


ST9316



Epidemiologie en Vaccin strategie

MenACWY IMD in België – Per leeftijdsgroep



Geconjugueerd vaccin Men ACWY: Bewezen groepsimmunitet

Wanneer vaccineren?

- Booster voor adolescentie
- MenC vervangen in schema? → Nog beter om vroeger te vaccineren

Epidemiologie en Vaccin strategie

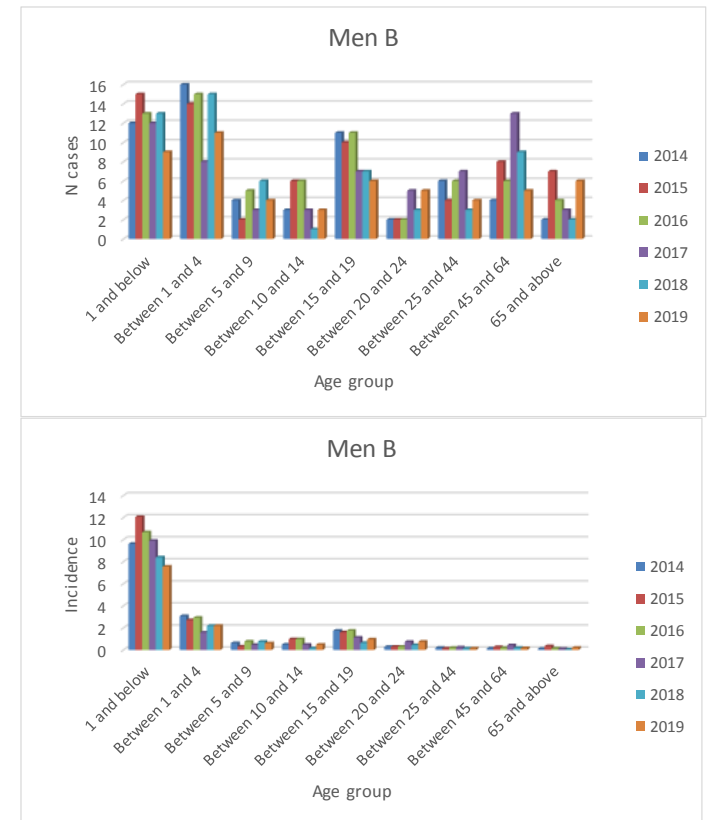
MenB IMD in België

MenB vaccin:

MenB capsule is niet-immunogeen → geen geconjugeerde vaccins mogelijk!

→ Recombinante proteïnen vaccins ontwikkeld:

- GSK's BEXSERO
- Pfizers Trumenba
- Tot nu geen bewezen groepsimmunitet effect
Wanneer vaccineren?
→ Hoe sneller, hoe beter! (2-4 maanden)



Epidemiologie en Vaccin strategie

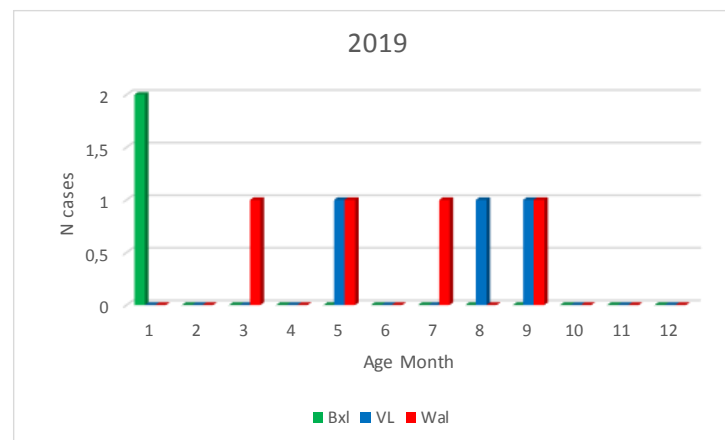
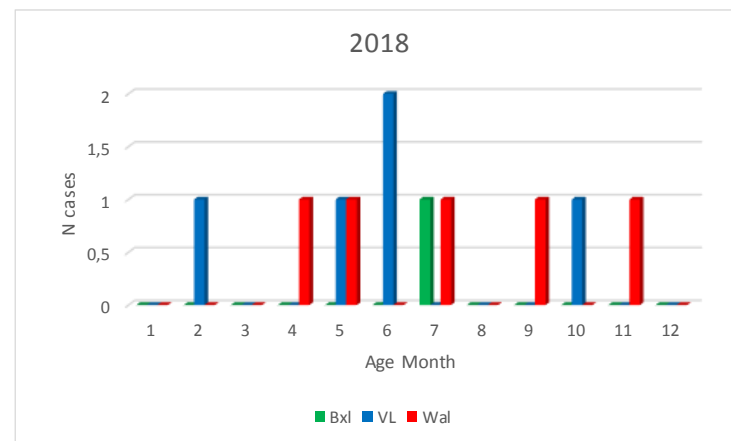
MenB IMD in België

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Epidemiologie en Vaccin strategie

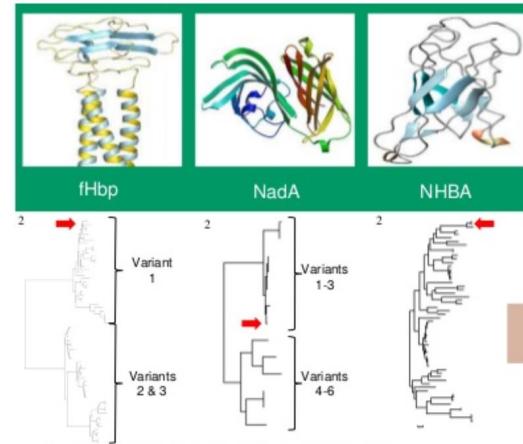
MenB of universeel IMD vaccin?

- Recombinante proteïnen vaccins
- Vaccin componenten ook aanwezig in andere serogroepen
- Potentiële bescherming tegen andere serogroepen:

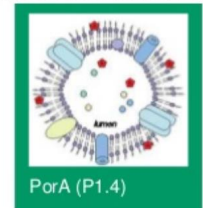
Effectiveness of Meningococcal B Vaccine against Endemic Hypervirulent *Neisseria meningitidis* W Strain, England

Shamez N. Ladhani, Marzia Monica Giuliani, [...], and Ray Borrow

Three recombinant proteins discovered by reverse vaccinology.



OMVs from the New Zealand outbreak strain (NZ 98/254).



PorA (P1.4)

249 VR1 variants³
649 VR2 variants⁴

Expression of proteins is variable

³<http://www.npham.com/news/101223/novartis-meningococcal-vaccine-besep>
⁴Vogel U et al. Lancet Infect Dis 2013;13:416-25.

The bivalent factor H binding protein meningococcal serogroup B vaccine elicits bactericidal antibodies against representative non-serogroup B meningococci

Shannon L. Harris ^a, Cuiwen Tan ^a, Lubomira Andrew ^a, Li Hao ^a, Paul A. Liberator ^a, Judith Absalon ^b, Annaliesa S. Anderson ^a, Thomas R. Jones ^a

**BEDANKT VOOR JULLIE
AANDACHT**