



Influenza H1N1 Pandemi Sikkerhedsovervågning af vaccinen

Doris Irene Stenver, MD, MPA
Overlæge, Forbrugersikkerhed
Medlem af EU's Bivirkningskomité





Oversigt

- ❑ Overvågning af (vaccine-)bivirkninger
 - ❑ Aktører, institutioner, strategier, værktøjer

- ❑ Danske bivirkningsdata på Pandemrix®
- ❑ Europæiske bivirkningsdata på Pandemrix®

- ❑ Sammenfatning





Danske aktører / institutioner

- Sundhedsstyrelsen
- Lægemiddelstyrelsen
- Statens Serum Institut

Ugentlige møder og ugentlige meddelelser om danske og europæiske bivirkningsdata





Statens Serum Institut´s opgaver Eksempler

- ❑ Distributør af vaccinen (ej indkøber)
- ❑ Overvågning af
 - ❑ Antal vaccinerede inden for de forskellige risikogrupper
 - ❑ Sygdomsaktivitet (praktiserende læger og vagtlæger rapporterer (sentinel), spørgeskema-undersøgelse af baggrundsforekomst)
 - ❑ Dødeligheden
 - ❑ Antal H1N1 – positive
 - ❑ Antal indlagte på intensivafdelinger og antal influenza-relaterede indlæggelser
- ❑ Deltager i forskningsprojekter
 - ❑ Baggrundsforekomst af forskellige sygdomme / potentielle bivirkninger, i samarbejde med European Centre for Disease Control





European Medicines Agency EMA – Docklands, London, etableret 1995





EU komiteer / netværk (1)

- ❑ Vurdering af registreringsansøgninger:
 - ❑ Committee of Human Medicinal Products (CHMP)
 - ❑ Koordinerer den centrale EU procedure (vaccinerne Pandemrix®, Celvapan® og Focetria®; Tamiflu®);
 - ❑ European Public Assessment Report (Q,E,S)
 - ❑ CMD(h)
 - ❑ Koordinerer mutual recognition (Relenza®) og decentrale procedurer (vaccinerne Panenza og Fluval P)
 - ❑ Pediatric Committee (PDCO)
 - ❑ Vurderer Pediatric Investigation Plans (PIPs)





EU komiteer / netværk (2)

- ❑ Overvågning af bivirkninger
 - ❑ EU´s bivirkningskomité (Pharmacovigilance WP)
 - ❑ Incident Review Network (virtuelt, rapid alert trigger)
 - ❑ Eudravigilance og Signal Detection Group
 - ❑ (Ugentligt) dataudtræk → nationale myndigheder
 - ❑ Pandemigruppe
 - ❑ EMA Pandemic Pharmacovigilance weekly updates





Overvågning af bivirkninger Dokumenter / værktøjer

- ❑ Periodiske Sikkerhedsopdaterings-rapporter (PSUR)
 - ❑ Overblik over sikkerhedsdata fra ALLE markeder / informationskilder
 - ❑ **Simplificeret PSUR koncept, månedlig indsendelse**

- ❑ Risk Management Plans (CHMP recommendations for pandemic vaccines)
 - ❑ Safety Specification (identified risks, potential risks...)
 - ❑ Pharmacovigilance Plan (routine + additional activities)
 - ❑ Risk Minimization Plan / Activities





Internationalt strategisk / fagligt samarbejde

- ❑ European Strategy for Influenza A / H1N1 Vaccine Benefit-Risk Monitoring
 - ❑ Joint strategy for European Medicines Agency, European Centre for Disease Control and Heads of Medicines Agency
 - ❑ Scope: All A/H1N1 vaccines effective against pandemic influenza virus, and licensed in the EU via any route of authorisation
 - ❑ Objective:
 - ❑ Define / describe activities necessary for R/B evaluation
 - ❑ Propose roles and responsibilities for different partners





European Strategy for Influenza A/H1N1 Vaccine Benefit–Risk Monitoring cont...

❑ Three pillars

- ❑ Safety – Effectiveness - Immunogenicity

❑ Stakeholders

- ❑ Vaccine manufacturers, Member States, Rapporteurs, CHMP and WPs, EMA, ECDC, research, clinical and public health centres....





European Strategy for Influenza A/H1N1 Vaccine Benefit–Risk Monitoring cont...

- ❑ **AESIs for A/H1N1 pandemic vaccines surveillance:**
 - ❑ Neuritis, convulsions*, anaphylaxis*, encephalitis*, vasculitis, Guillain-Barré syndrome, Bell´s palsy, demyelinating disorders, vaccination failure**
 - ❑ Case definitions existing* or being developed <http://brighoncollaboration.org>
 - ❑ Concept paper** on Vaccination Failure developed by CIOMS/WHO Working Group on Vaccine Pharmacovigilance <http://www.cioms.org>





European Strategy for Influenza A/H1N1 Vaccine Benefit–Risk Monitoring cont...

- ❑ Obligations - member states, example
 - ❑ Facilitate the notification of suspected ADRs by HCPs and patients, and **inform HCPs of adverse events of special interest** (AESIs), fatal and life-threatening events and other severe unexpected adverse reactions **to be reported in priority...**
 - ❑ **Not feasible in Denmark, due to national legislation**





European Centre for Disease Prevention and Control (ECDC, Stockholm)

❑ Roles / responsibilities

- ❑ Monitor effectiveness of pandemic vaccines (I-MOVE project)
- ❑ Collect background information on incidence of AESIs (VAESCO II project; ex. Guillain-Barre i DK)
- ❑ Develop linkage of population-based medical databases with immunisation registries across the EU (VAESCO II project)
- ❑ Establish an inventory of planned / ongoing studies in the EU relevant to risk / benefit evaluation





Indberetninger på sæson-influenza-vacciner 1. september 2009 - 8. januar 2010

- ❑ Ialt 30 indberetninger / 71 bivirkninger
 - ❑ Inluvac 32
 - ❑ Vaxigrip 25
 - ❑ Ukendt vaccine 14
 - ❑ Hyppigste SOC: General disorders and administration site conditions
 - ❑ Antal vaccinedoser: 585.000 (kilde SSI)





Danske bivirkningsdata på Pandemrix® (1)

*intensiv medieomtale af bivirkninger; **380.000 vaccinerede

Periode	Antal indberetninger (antal bivirkninger)
4. - 10. november	13 (34)
11. - 16. november	73 (280)
17. - 20. november*	87 (310)
21. - 27. november	149 (475)
28. november – 4. december	77 (224)
5. – 11. december	68 (173)
12. – 18. december**	48 (121)
I alt	515 (1617)





Danske bivirkningsdata på Pandemrix® (2)

System Organ Klasse	Antal bivirkninger
Generelle og reaktioner på vaccinationsstedet	591 (36.5 %)
Nervesystemet	247 (15.3 %)
Muskler og skelet	221 (13.7 %)
Mave-tarm	188 (11.6 %)
Huden	146 (9 %)
Luftveje	77 (4.5 %)





Danske bivirkningsdata på Pandemrix® (3)

- ❑ Alvorlige bivirkninger
 - ❑ 49 af de 515 indberetninger alvorlige (9.5%), bl.a.
 - ❑ 13 allergiske reaktioner
 - ❑ 10 neurologiske symptomer
 - ❑ 7 gastrointestinale symptomer
 - ❑ 2 tidlige aborter og en for tidlig fødsel af dødfødt barn
 - ❑ Kausalitetsvurdering, opfølgning, batch-monitorering
 - ❑ 6 dødsfald – ingen relation til vaccinen





European ADR data EMA Pandemic Update 6 January 2009

- ❑ Overall at least 29.4 million persons in the EEA, incl. 218.000 pregnant women, have been vaccinated
- ❑ The most frequent adverse reactions are expected and non-serious ADRs (reference: ADRs observed with Pandemrix H5N1)
- ❑ The B/R balance for pandemic vaccines remain positive





Centrally authorised vaccines ADR reports and patient exposure

- ❑ As of 27 December 2009 a total of **11.126 ADR** reports have been received by Eudravigilance
- ❑ As of 4 January 2010 **95.8 million doses** have been distributed in the EEA (**29.4 million vaccinated**)





Pandemrix® experience versus total

	Centrally authorised vaccines	Pandemrix®
Vaccine doses distributed (mio)	95.8	61.7 (64.4 %)
Number of individuals vaccinated (mio)	29.4	21.6 (73.5 %)
Number of ADR reports	11.126	8.129 (73.1 %)





Pandemrix®

* data from 4th EMA Pandemic Pharmacovigilance Update 23. December 2009)

❑ The most frequently reported SOCs

- ❑ General disorders and adm. site conditions (>4000*) (DK 1)
- ❑ Nervous System Disorders (>1700*) (DK 2)
- ❑ Gastrointestinal disorders (>1400*) (DK 4)
- ❑ Musculoskeletal disorders (>1100*) (DK 3)





Pandemrix cont...

- ❑ Pregnancy, puerperium, perinatal conditions (January 11, 2010)
 - ❑ 41 abortions
 - ❑ 16 intrauterine death
 - ❑ 9 still-birth





Pandemrix cont...

- ❑ Most frequently reported ADRs in children:
 - ❑ Pyrexia, hyperpyrexia, vomiting, injection site reaction, headache, fatigue, diarrhoea, cough, abdominal pain, decreased appetite, influenza-like illness, myalgia, rash, pain in extremity





Pandemrix cont...

- ❑ Fatal cases since authorisation
 - ❑ 107 cases identified (age range infancy – 101 year!)
 - ❑ In the majority of cases serious pre-existing conditions were reported, e.g. cardiovascular disease, pneumonia, renal insufficiency, sepsis, brain damage, ALS....





Adverse Events of Special Interest (AESIs) Examples

- ❑ Anaphylaxis – implemented in Pandemrix SmPC
- ❑ Multiple sclerosis – 11 cases (Pandemrix 9, Focetria 2)
- ❑ Guillain-Barre – 19 cases (Pandemrix 14, Focetria, 4, Celvapan 1)





Tamiflu®

- ❑ Patient exposure between 1 May 2009 – 30 November 2009: > 16 million patients
- ❑ A total number of 835 reports have been received worldwide, including at least 22 fatal cases
- ❑ ADR reports consistent with safety profile described in the product information
- ❑ Most frequently reported SOC's
 - ❑ Gastrointestinal disorders, skin and subcutaneous disorders, nervous system disorders, psychiatric disorders...





Sikkerhedsovervågning under pandemien Sammenfatning

- ❑ Vaccinernes B/R balance uforandret positiv
- ❑ Størst erfaringsgrundlag med Pandemrix®
- ❑ Europæiske bivirkningsdata som forventet
- ❑ God overensstemmelse mellem danske og europæiske data
- ❑ Omfattende nationalt og internationalt samarbejde etableret / videreudviklet (koordinering af aktiviteter, arbejdsdeling, gennemsigtighed...)
- ❑ Perspektiver på længere sigt?



LÆGEMIDDEL
STYRELSEN

DANISH MEDICINES AGENCY

