Experiences with hospital-based approach to investigate serious and rare vaccine adverse events

Silvia Perez-Vilar, PharmD, PhD
Center for Biologics Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)
August 24, 2017
Disclaimer

My comments are an informal communication and represent my own best judgment. These comments do not bind or obligate the US FDA.
Background

There is a need to enhance vaccine pharmacovigilance globally

Serious and rare vaccine adverse events call for multi-country collaborative hospital-based approaches
Roadmap for the international collaborative epidemiologic monitoring of safety and effectiveness of new high priority vaccines

Hector S. Izurieta a,*, Patrick Zuber b, Jan Bonhoeffer c,d, Robert T. Chen e, Osman Sankoh f,g,h, Kayla F. Laserson i, Miriam Sturkenboom j, Christian Loucq k, Daniel Weibel j, Caitlin Dodd l, Steve Black l

a Food and Drug Administration (FDA), MD, United States
b World Health Organization, Geneva, Switzerland
c Brighton Collaboration Foundation, Basel, Switzerland
d University Children’s Hospital Basel, University of Basel, Basel, Switzerland
e Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States
f INDEPTH Network, Accra, Ghana
g School of Public Health, University of the Witwatersrand, Johannesburg, South Africa
h Hanoi Medical School, Hanoi, Viet Nam
i KEMRI/CDC Research and Public Health Collaboration, Kisumu, Kenya
j Erasmus University Medical Center, Rotterdam, The Netherlands
k International Vaccine Institute, Seoul, Republic of Korea
l University of Children’s Hospital, University of Cincinnati, OH, United States
LET'S TRY
Study objectives

Demonstrate the feasibility and utility of global collaboration in the assessment of vaccine safety, including countries both with and without an established infrastructure for vaccine active safety surveillance.

Assess the risk of Guillain-Barre Syndrome following pH1N1 vaccination.
# Global H1N1 consortium

## Characteristics of databases included in primary or sensitivity analyses by country.

<table>
<thead>
<tr>
<th>Country</th>
<th>Database</th>
<th>Dates of observation</th>
<th>Number of cases</th>
<th>Case ascertainment</th>
<th>Vaccination status ascertainment</th>
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<tr>
<td>Australia</td>
<td>Adelaide</td>
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<td>Vaccine Registry, Self-Report, Outpatient Chart Review</td>
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<td>Quebec</td>
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<td>Administrative database, active prospective surveillance</td>
<td>Vaccine registry</td>
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<td>Denmark</td>
<td>Shanghai</td>
<td>1/1/2009–7/1/2010</td>
<td>22</td>
<td>Administrative database</td>
<td>Outpatient Chart Review</td>
</tr>
<tr>
<td>Finland</td>
<td></td>
<td>11/1/2009–11/1/2010</td>
<td>31</td>
<td>National Patient Register using primary discharge diagnoses</td>
<td>Vaccine Registry</td>
</tr>
<tr>
<td>Finland</td>
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<td>11/1/2009–11/1/2010</td>
<td>29</td>
<td>Hospital discharge and hospital outpatient records, primary diagnoses</td>
<td>Vaccine registry</td>
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<td>The Netherlands</td>
<td>IPCI</td>
<td>11/1/2009–11/1/2010</td>
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<td>Identified prospectively through neurologists</td>
<td>GP(^{\text{a}}) medical record</td>
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<td>NNI/TSSH</td>
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<td>Administrative Database</td>
<td>Hospital Medical Records</td>
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<td>Spain</td>
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<td>11/1/2009–11/1/2010</td>
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<td>Automated GP records</td>
<td>GP(^{\text{a}}) records</td>
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<tr>
<td>The United Kingdom</td>
<td>CPRD(^{\text{a}})</td>
<td>11/1/2009–4/30/2010</td>
<td>6</td>
<td>Electronic Medical Records</td>
<td>Vaccine Registry</td>
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<tr>
<td>The United States</td>
<td>DoD(^{\text{a}})</td>
<td>11/1/2009–4/30/2010</td>
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<td>Electronic Medical Records</td>
<td>Administrative Database</td>
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<td>PRISM(^{\text{a}})</td>
<td>10/22/2009–8/7/2010</td>
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<td>Vaccine Registries and Claims Databases</td>
<td>Electronic Medical Claims</td>
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<td>VA(^{\text{a}})</td>
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<td>Vaccine Registry and Administrative database</td>
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<td>Administrative Database</td>
<td>Administrative database</td>
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Global H1N1 consortium

<table>
<thead>
<tr>
<th>Country</th>
<th>Database</th>
<th>Criteria for exclusion</th>
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<tr>
<td>Excluded databases</td>
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<td>Patient Consent Required (potential bias)</td>
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<td>France</td>
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<td>Israel</td>
<td>Maccabi</td>
<td>Relative incidence found to be an outlier compared to all other study site relative incidence findings</td>
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<td>Data were obtained solely from a specialist network (potential bias)</td>
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<td>Mexican States</td>
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<td>Norway</td>
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<td>Patient consent required with potential bias</td>
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<td>Sweden</td>
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</table>
Analytic Methods

Self-controlled case series methods

- Classical SCCS
- SCRI
- Pseudo-likelihood approach

Day 1  Day 42
### GBS risk following H1N1 vaccination

#### Pooled analyses

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Risk window(s)</th>
<th>Exclusions</th>
<th>Brighton criteria levels</th>
<th>Relative incidence</th>
<th>Confidence interval</th>
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<tr>
<td><strong>Primary analysis</strong></td>
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<tr>
<td>Standard self-controlled case series (SCCS)</td>
<td>Days 1–42</td>
<td>● Databases (DBs) with vaccinated cases only</td>
<td>1–3</td>
<td>2.42</td>
<td>(1.58, 3.72)</td>
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<td><strong>Sensitivity analyses</strong></td>
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<td>1–4A</td>
<td>2.83</td>
<td>(1.91, 4.19)</td>
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<td>Standard SCCS</td>
<td>Days 1–42</td>
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<td>1–2</td>
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<td>(1.48, 3.70)</td>
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<td>Standard SCCS</td>
<td>Days 1–42</td>
<td>● DBs with vaccinated cases only</td>
<td>1–3</td>
<td>2.88</td>
<td>(1.79, 4.65)</td>
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<td>● Cases with reported URI or ILI in the 30 days before diagnosis</td>
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<td>(1.75, 4.26)</td>
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<td>(1.42, 3.52)</td>
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<td>1–4A</td>
<td>2.59</td>
<td>(1.72, 3.90)</td>
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<td>Days 1–42</td>
<td>● Unvaccinated cases</td>
<td>1–3</td>
<td>2.37</td>
<td>(1.47, 3.85)</td>
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<td></td>
<td>● Cases vaccinated after diagnosis</td>
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<td>Standard SCCS</td>
<td>Days 1–7* 8–21* 22–42*</td>
<td>● DBs with vaccinated cases Only</td>
<td>1–3</td>
<td>2.61</td>
<td>(1.17, 5.84)</td>
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<td>● DBs with vaccinated cases Only</td>
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<tr>
<td>Vaccinated cases only</td>
<td>Days 1–42</td>
<td>● Unvaccinated cases</td>
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<td>1.88</td>
<td>(1.04, 3.41)</td>
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<td>● Cases vaccinated after diagnosis</td>
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<td></td>
<td></td>
<td>● Non-adjuvanted vaccine recipients</td>
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<td>Vaccinated cases only</td>
<td>Days 1–42</td>
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<td>2.97</td>
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<td>● Cases vaccinated after diagnosis</td>
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<td></td>
<td>● Adjuvanted vaccine recipients</td>
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</tbody>
</table>

Dodd et al, Vaccine 2013
## GBS risk following H1N1 vaccination

### Meta-analytic approach

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Risk window(s)</th>
<th>Exclusions</th>
<th>Brighton criteria levels</th>
<th>Relative incidence</th>
<th>Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-controlled case series (SCCS)</td>
<td>Days 1–42</td>
<td>- Databases (DBs) with vaccinated cases only</td>
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<td>2.09</td>
<td>(1.28, 3.42)</td>
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<td>Vaccinated cases only</td>
<td>Days 1–42</td>
<td>- Unvaccinated cases excluded</td>
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<td>Vaccinated cases only adjuvanted</td>
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<td>- Cases vaccinated after diagnosis</td>
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<td>1.65</td>
<td>(0.86, 3.19)</td>
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<td>Vaccinated cases only non-adjuvanted</td>
<td>Days 1–42</td>
<td>- Non-adjuvanted vaccine recipients</td>
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<td>3.10</td>
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<tr>
<td></td>
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<td>- Unvaccinated cases</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>- Cases vaccinated after diagnosis</td>
<td></td>
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</tr>
</tbody>
</table>

Dodd et al, Vaccine 2013
## Conclusions

- **Multi-country collaborations are feasible**
- **Useful platform to evaluate vaccine safety concerns**
- **Ability to contrast risks between countries/vaccine products**
- **Hypothesis-generation**
- **Support association between GBS and pH1N1 vaccination**

Dodd et al, Vaccine 2013
International collaboration to assess the risk of Guillain Barré Syndrome following Influenza A (H1N1) 2009 monovalent vaccines

Caitlin N. Dodd a,⁎, Silvana A. Romio b, Steven Black c, Claudia Vellozzi d, Nick Andrews e, Miriam Sturkenboom b, Patrick Zuber f, Wei Hua g, Jan Bonhoeffer h, i, Jim Buttery j, Nigel Crawford k, Genevieve Deceuninck l, Corinne de Vries m, Philippe De Wals l, M. Victoria Gutierrez- Gimeno n, Harald Heijbel o, Hayley Hughes p, Kwan Hur q, Anders Hviid r, Jeffrey Kelman s, Tehri Kilpi t, S.K. Chuang u, Kristine Macartney v, Melisa Rett w, Vesta Richardson Lopez-Callada x, Daniel Salmon y, z, Francisco Gimenez Sanchez aa, Nuria Sanz bb, Barbara Silverman cc, Jann Storsaeter dd, Umapathi Thirugnanam ee, Nicoline van der Maas ff, Katherine Yih w, Tao Zhang gg, Hector Izurieta h, the Global H1N1 GBS Consortium l
Lessons learned

- Unbiased case retrieval
- Degree to which sites were able to review charts and ascertain important covariates
- Centralized case adjudication
- Improved data quality control
- Closer supervision of data abstraction and case ascertainment
- More participation of low and middle-income countries
Global Vaccine Safety Initiative

Proof-of-concept study on aseptic meningitis and immune thrombocytopenic purpura following measles-mumps-containing vaccines
Study goals and outcomes

To assess the feasibility of a hospital-based global collaboration through the assessment of two well-known vaccine associations

• Aseptic meningitis following mumps-containing vaccines
• ITP following measles-containing vaccines

Using a common protocol and case report forms

• Common training tools
• Using a central data repository with state of the art protection of patient information
Selection of participating sites

- Large catchment area
- Specialty services
- Coding system for discharge diagnosis (ICD9 or 10)
- Access and capacity to link clinical, laboratory and immunisation information
- Commitment to participate
- Agreement on network management principles
- Demonstrated capacity to access discharge diagnosis and immunisation records

43 institutions from 24 countries contacted

32 institutions from 21 countries expressed interest and fulfilled minimal eligibility criteria

32 institutions from 21 countries to complete the site capacity exercise

26 institutions from 16 countries fully eligible

Project collaboration agreement; Institutional/national clearance

Site survey

Site capacity exercise

Tools
GVS MCC network

26 sentinel sites (49 hospitals) distributed in 16 countries of the six WHO regions

Perez-Vilar S et al, Vaccine 2017

Disclaimer: Lines on the map represent approximate border lines for which there may not yet be full agreement.
GVS-MCC network
The Americas
Training of sites

- Training webinars
- Field trips to Iran, India & Uganda
- Face to face training for all PAHO region sites
- Manual of Procedures for data collection methods
- Videos of the tools for data entry, case classification and data sharing
- Close monitoring of the sites
- Dummy case abstraction training and submissions and feedback
- Initial data submission & quality control
Analytic Methods

Self-controlled risk interval

Day 1
Day 42
Day 43
Day 84

Case crossover

Day 270

Day -85

Day -43

Index date

Control period
Risk period
Wash-out period

Control window
Case window
Results

Aseptic meningitis
- 84 confirmed cases
  - SCRI: n=51
  - CCO: n=73

ITP
- 183 confirmed cases
  - SCRI: n=55
  - CCO: n=152
# MMR Vaccine types

<table>
<thead>
<tr>
<th>Vaccine product</th>
<th>Measles strain</th>
<th>Mumps strain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Priorix®, GlaxoSmithKline Biologicals</td>
<td>Schwarz</td>
<td>RIT 4385*</td>
</tr>
<tr>
<td>Priorix Tetra®, GlaxoSmithKline Biologicals</td>
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<td>Shanghai-191</td>
<td>S79</td>
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<td>Measles, Lanzhou Institute of Biological Products Co., Ltd.</td>
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<td>Measles-Rubella, Beijing Tiantan Biological Products, Co., Ltd.</td>
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<td>M-M-R-II®, Merck Sharp &amp; Dohme Corp.</td>
<td>Enders’ Edmonston</td>
<td>Jeryl Lynn (Level B)</td>
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<td>AIK-C</td>
<td>Hoshino</td>
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<td>Tresivac®, Serum Institute of India Pvt. Ltd</td>
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<tr>
<td>Rouvax®, Sanofi Pasteur</td>
<td>Schwarz</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: MMR (measles-mumps-rubella); * Derived from Jeryl Lynn strain
Risk of aseptic meningitis following mumps-containing vaccines

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Overall (any strain)

SCRI: IRR= 10.9; 95% CI= 4.2-27.8

CCO: OR= 35.0; 95% CI= 4.8-256

Strain specific SCRI

Hoshino/LZ/Urabe (Iran only): IRR= 20.3; 95% CI= 4.8-85

Leningrad-Zagreb: IRR=10.8; 95% CI= 1.3-87.4

RIT 4385/Jeryl Lynn: Non-estimable
Risk of ITP following measles-containing vaccines

Perez-Vilar S et al, Vaccine 2017

Overall (any strain)
- SCRI: IRR = 5.0; 95% CI = 2.5-9.7
- CCO: OR = 4.7; 95% CI = 2.1-10.7

Strain-specific SCRI
- **AIK-C/Edmonston-Zagreb/Schwarz (Iran):**
  - IRR: 0.51; 95% CI: 0.10-2.54

- **Edmonston-Zagreb**
  - IRR: 11.1; 95% CI: 1.4-90.3

- **Enders’Edmonston**
  - IRR: 8.5; 95% CI: 1.9-38.1

- **Schwarz**
  - IRR=20.7; 95% CI: 2.7-157.6

**Shanghai-191**
Non-estimable
Conclusions

The study demonstrated that a hospital-based collaboration to evaluate vaccine safety using a common protocol across diverse countries with high participation of LMICs is feasible.

Valid data were generated and known associations were confirmed.

Potential to characterize differences in risk between vaccine strains/products using a common protocol.

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Survey on sites experience

- Involvement in protocol development: 4.09
- Easiness of getting ethical approval: 3.61
- Easiness of identifying cases: 3.70
- Access to vaccination status: 3.22
- Training on study protocol: 4.30
- Communication during the project: 4.00
- Willingness to participate in subsequent project: 4.79

Guillard-Maure C et al, Vaccine 2017
Lessons learned

- Electronic hospital discharge databases
- Access to vaccination records
- No internet access limitations
- Shorter follow-up periods
- Reduction lag times between simulation exercises, training, start of data collection
- On-site monitoring at the very beginning of data collection
- Large referral hospitals
- Inclusion of sites from tropical/sub-tropical areas
References

Enhancing global vaccine pharmacovigilance: Proof-of-concept study on aseptic meningitis and immune thrombocytopenic purpura following measles-mumps containing vaccination

Silvia Perez-Vilar\textsuperscript{a,b,*}, Daniel Weibel\textsuperscript{a,c}, Miriam Sturkenboom\textsuperscript{a}, Steven Black\textsuperscript{d}, Christine Maure\textsuperscript{a}, Jose Luis Castro\textsuperscript{a}, Pamela Bravo-Alcántara\textsuperscript{a}, Caitlin N. Dodd\textsuperscript{a}, Silvana A. Remio\textsuperscript{a}, Maria de Rodder\textsuperscript{e}, Swabra Nakaro\textsuperscript{f}, Helvert Felipe Molina-León\textsuperscript{g}, Varalakshmi Elango\textsuperscript{h}, Patrick L.F. Zuber\textsuperscript{i}, the WHO Global Vaccine Safety-Multi Country Collaboration\textsuperscript{a}

Operational lessons learned in conducting a multi-country collaboration for vaccine safety signal verification and hypothesis testing: The global vaccine safety multi country collaboration initiative

Christine Guillard-Maure\textsuperscript{a}, Varalakshmi Elango\textsuperscript{h}, Steven Black\textsuperscript{d}, Silvia Perez-Vilar\textsuperscript{a}, Jose Luis Castro\textsuperscript{a}, Pamela Bravo-Alcántara\textsuperscript{a}, Helvert Felipe Molina-León\textsuperscript{g}, Daniel Weibel\textsuperscript{a}, Miriam Sturkenboom\textsuperscript{a}, Patrick L.F. Zuber\textsuperscript{i}, the WHO Global Vaccine Safety-Multi Country Collaboration\textsuperscript{a}

Building capacity for active surveillance of vaccine adverse events in the Americas: A hospital-based multi-country network

Pamela Bravo-Alcántara\textsuperscript{a}, Silvia Pérez-Vilar\textsuperscript{b,c}, Helvert Felipe Molina-León\textsuperscript{g}; Miriam Sturkenboom\textsuperscript{b,d}, Steven Black\textsuperscript{d}, Patrick L.F. Zuber\textsuperscript{i}, Christine Maure\textsuperscript{a}, Jose Luis Castro\textsuperscript{a}, on behalf of the L.A.N.V.A.P. (Latin American Network for Vaccine Pharmacovigilance)\textsuperscript{a}
Acknowledgments

WHO
Christine Maure
Varalakshmi Elango
Patrick L.F. Zuber

PAHO/WHO
Jose Luis Castro
Pamela Bravo-Alcántara
Helvert Felipe Molina-León

Erasmus MC
Daniel Weibel*
Miriam Sturkenboom*
Caitlin N. Dodd
Silvana A. Romio
Maria de Ridder
Swabra Nakato

Cincinnati Children’s Hospital
Steven Black*

*Vaccine.GRiD

GRiP-FP7 EC

FDA
Hector S. Izurieta
Gopa Raychaudhuri
Steven Anderson
Chris Jankosky

WHO Global Vaccine Safety-Multi Country Collaboration

Albania: Georgina Kuli-Lito, Entela Kostaqi, Elizana Petrela, (University Hospital Center Mother Theresa)

Argentina: Vanesa E. Castellano (Hospital de Niños Ricardo Gutiérrez, Buenos Aires), Lucía Chiavetti (Hospital José Bernardo Iturraspe), Adriana Falcó (Hospital Público Materno Infantil), Angela Gentile (Hospital de Niños Ricardo Gutiérrez), Karina Guirau (Hospital Pediátrico Dr. Avelino L. Castelán), María Eugenia Pérez Carrega (Ministerio de Salud de la Nación), Susana Rasjido (Hospital Regional Teodoro J. Schestakow), Sofía Testino (Hospital Zonal Trelew Dr. Adolfo Margara), Carla Vizzotti (Ministerio de Salud de la Nación)

Australia: Jim Buttery (Murdoch Children’s Research Institute & Monash Health), Alissa Mcminn (Murdoch Children’s Research Institute), Julie Quinn (Monash Health)

Chile: Marcela Avendaño (Ministerio de Salud), Marcela González (Hospital Dr. Gustavo Fricke), Rosanna Lagos (Hospital de Niños Roberto del Río), Marcelo Maturana (Hospital Clínico Regional Guillermo Grant Benavente), Fernando Muñoz (Ministerio de Salud), Adiela Saldaña (Instituto de Salud Pública), Guillermo Soza (Hospital Regional de Temuco Dr. Hernán Henríquez Aravena)

China: Tao Zhang, Xiyan Zhang (Fudan University), Yunfang Ding (Suzhou University Affiliated Children Hospital), Jun Zhang (Suzhou Center for Disease Control and Prevention)

Colombia: Martha I. Alvarez-Olmos (Fundación Cardioinfantil), Luz Amparo Sastoque (Instituto Nacional de Salud)

Costa Rica: Marcela Hernández-de Mezerville (Hospital Nacional de Niños Dr Carlos Sáenz Herrera), Vicenta Machado (Caja Costarricense de Seguro Social), Ileana Roversi (Ministerio de Salud), Angélica Vargas Camacho (Caja Costarricense de Seguro Social)

Honduras: Marco Tulio Luque (Hospital Escuela Universitaria), Liset Mendoza (Ministerio de Salud)

India: Mandyam Ravi, V.G. Manjunath (JSS University)

Iran: Abdollah Karimi, Roxana Mansour Ghanai, Kimia Seifi, Fariba Shirvani (Mofid Children hospital, Pediatric Infectious Disease Research Center; Shahid Beheshti University of Medical Sciences), Mahmoud Reza Ashrafi, Nima Parvaneh, Leily Kochakzadeh, Sertareh Mamishi, Farzad Kompani, Hamid Eshaghi, Vahideh Pirmoazen (Children’s Medical Center Pediatric Center of Excellence; Tehran University of Medical Sciences)

Perú: Renne F. Aquije Hernández (Ministerio de Salud, Maria Esther Castillo Díaz (Instituto Nacional de Salud del Niño), Gladys Turpo Mamani (Centro Nacional de Epidemiología, Prevención y Control de Enfermedades, MINSA)

Singapore: Koh Cheng Thoon (KK Women’s & Children’s Hospital), Bee Khiam Oh (KK Women’s & Children’s Hospital) Yelen (KK Women’s & Children’s Hospital)

South Africa: Clare Cutland, Shabir A. Madhi, Michelle Groome, Sithembiso Velaphi, Alane Izu, Linh Diep, Cleopas Hwinya (Chris Hani-Baragwanath Hospital, Johannesburg)

Spain: Silvia Pérez-Vilar, Javier Diez-Domingo, Marian Martín-Navarro, Esther Soriano-Garcia (FISABIO)

Uganda: Stephen Legesi Pande, Florence Alaroker, Dorothy Amulen, Margaret Akareut, Esther Areto, Richard Samson Komo, Ogwang Quinto (Soroti Regional referral Hospital)

Uruguay: Gustavo Giachetto, Noelia Speranza, Carlos Zunino (Centro Hospitalario Pereira Rossell)
WHAT'S NEXT?
Acknowledgments

Mikhail Menis
Hector S Izurieta
Chris Jankosky
Deepa Arya
Richard Forshee