Monitoring Influenza/COVID-19 Vaccine Effectiveness in Europe – from I-MOVE to VEBIS: Measuring vaccine effectiveness since 2008-09

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19 April 2024

We have received funding from ECDC, WHO/Europe, European Commission for these studies.

We declare no conflict of interest.

Travel and accommodation to this meeting was self-funded.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101003673

European Union

Motivation

Why do we need vaccine effectiveness studies?

- Vaccine efficacy (randomised control trial) and
  vaccine effectiveness (observational data) estimates may differ due to
  - populations (e.g. healthy vs whole population)
  - field conditions (e.g. cold chain, timing of doses)

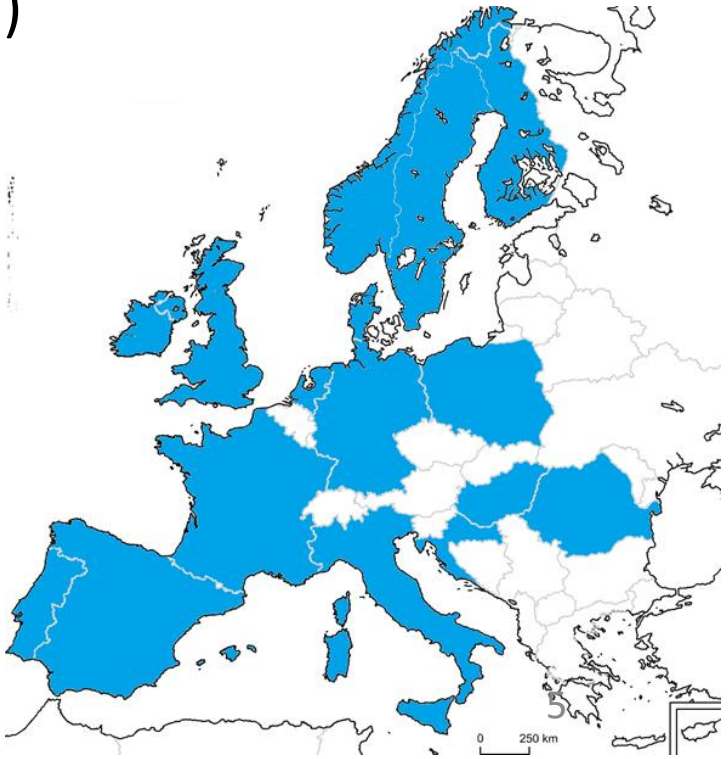
- Vaccination-induced protection may also vary by
  - different risk groups
  - severity of disease
  - emergence of new strains
  - vaccine-related parameters

- Need for rapid information to inform policy decisions
  - definition of target groups for vaccination
  - timing of vaccination campaign and booster doses/re-vaccination
  - need for a new vaccination campaign with the emergence of new strains
  - re-formulation of subsequent vaccines

Background I-MOVE and related studies

Background I-MOVE and related multicentre VE studies

- Vaccine evaluation research in the EU 2007–2022 (now under ECDC VEBIS umbrella)
- Over 20 study site and partner national/regional public health institutes in Europe
- >100 publications in peer-reviewed journals (national and pooled studies)
- International collaboration (US, Canada, Hong Kong, Australia)
- Capacity development (Masters, PhD, EPIET/FETP)
- Public funding only
- Inspiration for other international muticentre VE networks Euro-SAVE, AFRO-MoVE
- Well-established, robust network: estimating influenza VE during challenges of COVID-19 pandemic (2021–22)



I-MOVE, I-MOVE+, I-MOVE-COVID-19 and VEBIS studies

2008-2022						YEAR
Project	**Funding**	**Disease**	**Setting**	**Study design**	**Population**	**08 09 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24**
I-MOVE	ECDC	Flu	Primary care	TND	≥65y	
		Flu	Primary care	TND	All ages	
I-MOVE+	Horizon 2020	Flu	Hospital	TND	≥65y	
		Pneumo	Hospital	Broome;Cohort	≥65y	
I-MOVE-COVID-19	Horizon 2020	COVID-19	Primary care	TND	All ages	
		COVID-19	Hospital	TND	All ages	
Now: VEBIS 2021 onwards						
VEBIS Lot 1	ECDC	COVID-19	Hospital	TND	All ages	
		Influenza	Hospital	TND	All ages	
VEBIS Lot 2	ECDC	COVID-19	Hospital	Cohort	HCW	
		Influenza	Hospital	Cohort	HCW	
VEBIS Lot 4	ECDC	COVID-19	EHR	Cohort	All ages	
VEBIS Lot 5	ECDC	COVID-19	Primary care	TND	All ages	
		Influenza	Primary care	TND	All ages	

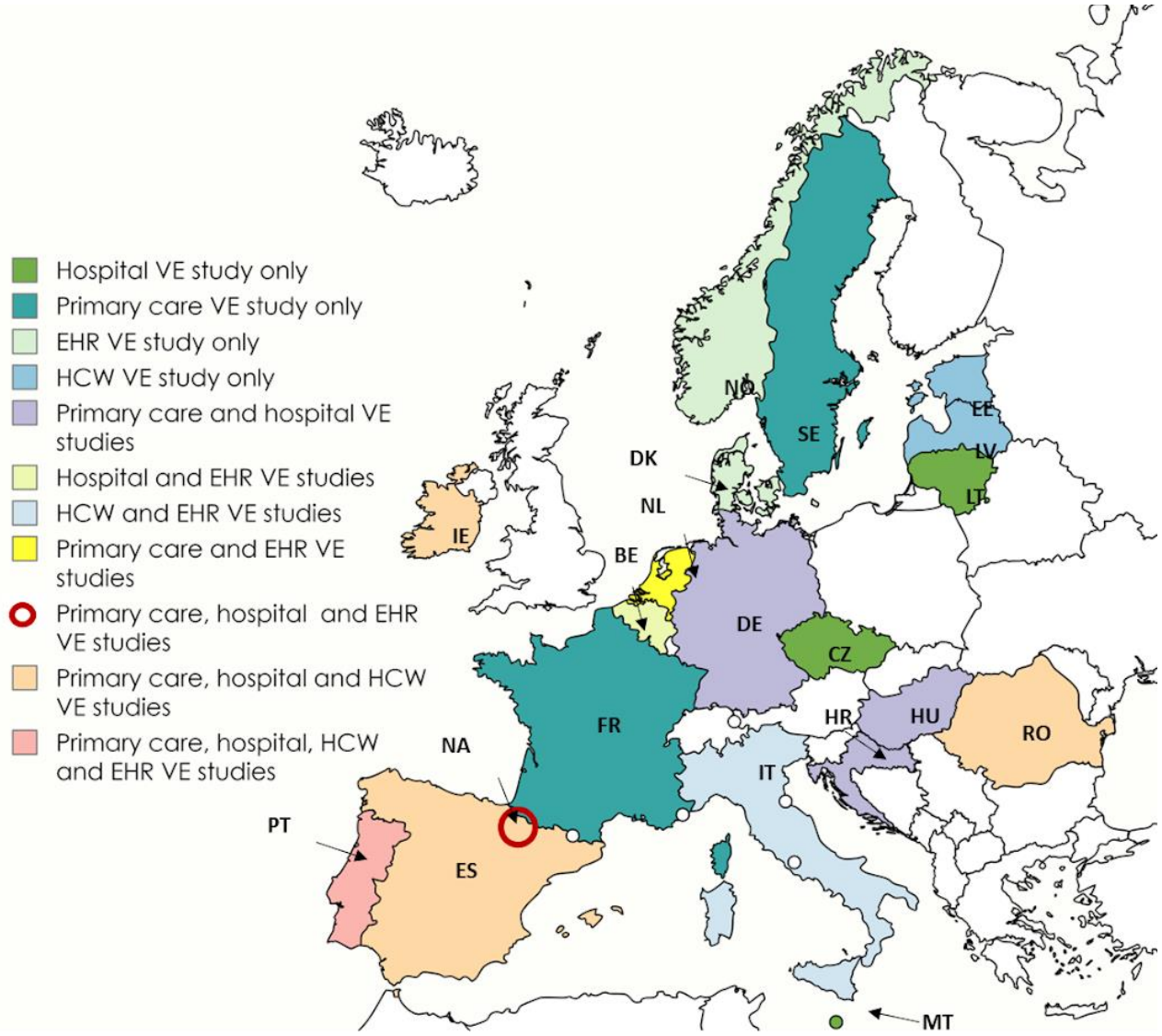
TND: test negative design

Overview of VEBIS studies

VEBIS Programme

- VEBIS: Vaccine Effectiveness, Burden and Impact Studies
  - funded by ECDC since October 2021
  - Hospital and primary care TND studies were based on I-MOVE/I-MOVE+/I-MOVE-COVID-19 networks
- Primary objective: to estimate COVID-19 and influenza VE in the EU/EEA
  - overall and by vaccine product
- Studies established in four different EU/EEA settings/populations
  - test-negative design (among community-dwelling population)
    - primary care attendees with acute respiratory infection (ARI)
    - patients hospitalised with severe acute respiratory infection (SARI)
    - many studies embedded in existing ARI/SARI surveillance systems
  - cohort studies
    - electronic health register (EHR) based cohorts of community-dwelling individuals eligible for COVID-19 vaccination. Outcome: COVID-19-related hospitalisations or deaths
    - healthcare worker (HCW) cohorts. Outcome: SARS-CoV-2 or influenza infection

VEBIS primary care, hospital, EHR and HCW studies include 20 study sites across 19 countries



VEBIS primary care and hospitalised patients, electronic health register (EHR) and healthcare worker (HCW) studies: methods

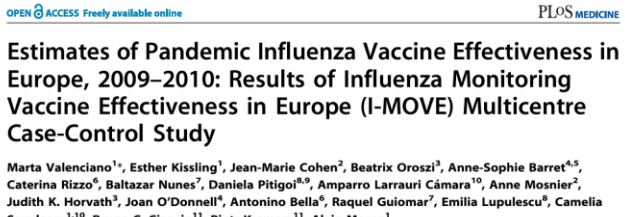
- All studies employed
  - Generic common protocol pooling multi-country results
  - Case definition: PCR-confirmed SARS-CoV-2/influenza infection
  - Included only those that were eligible for vaccination and provided consent
  - Estimates adjusted for key confounders (often age, sex, site, time and underlying condition)
- Differences between studies:

Characteristic	Primary care	Hospitalised	Population-based EHRs	HCWs
Study type	Test-negative, case–control design with some studies nested in surveillance		Retrospective cohort	Prospective cohort
Population	Community eligible for booster vaccination			Hospital-working HCWs
Case definition	Symptomatic infections (ARI/ILI)	Hospitalised (SARI)	Hospitalisation (SARI) or death	All symptomatic or asymptomatic infections
Age-groups	≥5 years; vaccine target group		≥ 65 years	Adults (working age)
Analysis	Logistic regression: VE=(1-aOR)*100		Cox regression: VE=(1-aHR)*100 (HR: hazard ratio)	

Key research questions 2008–2024

Informing those who need to know in a timely way

- Initiation of the **GIVE report** (Global influenza vaccine effectiveness report)
  - Report of influenza TND VE results from studies across the world
  - Informs WHO influenza vaccine strain selection committee meeting
  - Produced twice a year: February and September → Northern and Southern Hemisphere vaccines
  - First report: September 2013
  - Over the years up to 17 studies reporting from all continents
  - Also includes clade-specific VE
- Early influenza VE 2023 (primary care) – HTML report in December to stakeholders (MoH, institute of public health, network of GPs)
- Pandemic VE: 2009 influenza VE; first COVID-19 vaccines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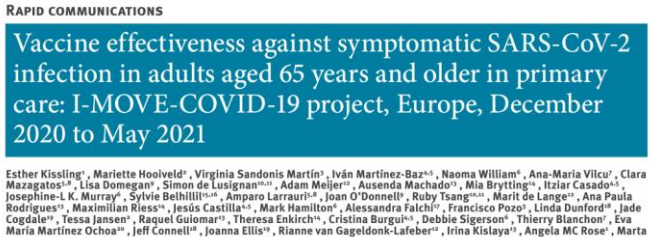
Estimates of Pandemic Influenza Vaccine Effectiveness in Europe, 2009–2010: Results of Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) Multicentre Case-Control Study

Marta Valenciano[1*], Esther Kissling[1], Jean-Marie Cohen[2], Beatrix Oroszi[3], Anne-Sophie Barret[4,5], Caterina Rizzo[6], Baltazar Nunes[7], Daniela Pitigoi[8,9], Amparo Larrauri Cámara[10], Anne Mosnier[2], Judith K. Horvath[3], Joan O'Donnell[4], Antonino Bella[6], Raquel Guiomar[7], Emilia Lupulescu[8], Camelia


RAPID COMMUNICATIONS

Vaccine effectiveness against symptomatic SARS-CoV-2 infection in adults aged 65 years and older in primary care: I-MOVE-COVID-19 project, Europe, December 2020 to May 2021

Esther Kissling[1], Mariette Hooiveld[2], Virginia Sandonis Martín[1], Iván Martínez-Baz[4,5], Naoma William[4], Ana-Maria Vilcu[7], Clara Mazagatos[5,8], Lisa Domegan[9], Simon de Lusignan[10,11], Adam Meijer[12], Ausenda Machado[13], Mia Brytting[14], Itziar Casado[4,5], Josephine-L K. Murray[6], Sylvie Behillil[15,16], Amparo Larrauri[5,8], Joan O'Donnell[9], Ruby Tsang[10,11], Marit de Lange[12], Ana Paula Rodrigues[13], Maximilian Riess[14], Jesús Castilla[4,5], Mark Hamilton[9], Alessandra Falchi[17], Francisco Pozo[1], Linda Dunford[18], Jade Cogdale[19], Tessa Jansen[2], Raquel Guiomar[13], Theresa Enkirch[14], Cristina Burgui[4,5], Debbie Sigerson[6], Thierry Blanchon[7], Eva María Martínez Ochoa[20], Jeff Connell[18], Joanna Ellis[19], Rianne van Gageldonk-Lafeber[12], Irina Kislaya[13], Angela MC Rose[1], Marta

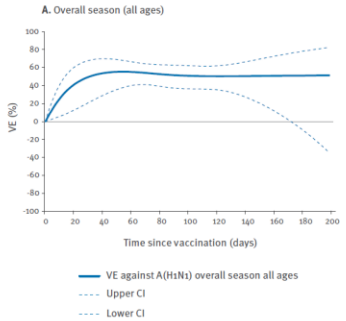
VE by time since vaccination

- VE by time since vaccination helps us understand potential decline in VE
  - Due to waning of immunity, virological changes
- Informs public health policy: Timing of vaccination campaigns, possible second vaccinations
- Influenza VE by time since vaccination from 2011–2012

RESEARCH ARTICLE

I-MOVE multicentre case–control study 2010/11 to 2014/15: Is there within-season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination?

E Kissling [1], B Nunes [2], C Robertson [3 4 5], M Valenciano [1], A Reuss [6], A Larrauri [7 8], JM Cohen [9], B Oroszi [10], C Rizzo [11], A Machado [2], D Pitigoi [12 13], L Domegan [14], I Paradowska-Stankiewicz [15], U Buchholz [6], A Gherasim [7], I Daviaud [9], JK Horváth [10], A Bella [11], E Lupulescu [12], J O´Donnell [14], M Korczyńska [15], A Moren [1], I-MOVE case–control study team [16]

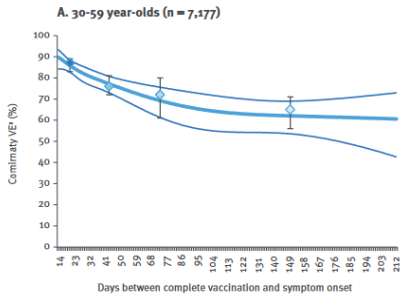


- COVID-19 VE by time since vaccination as part of each publication

RESEARCH

Effectiveness of complete primary vaccination against COVID-19 at primary care and community level during predominant Delta circulation in Europe: multicentre analysis, I-MOVE-COVID-19 and ECDC networks, July to August 2021

Esther Kissling[1], Mariëtte Hooiveld[2], Iván Martínez-Baz[3,4], Clara Mazagatos[4,5], Naoma William[6], Ana-Maria Vilcu[7], Marjolein N Kooijman[8], Maja Ilić[9], Lisa Domegan[10], Ausenda Machado[11], Simon de Lusignan[12,13], Mihaela Lazar[14], Adam Meijer[8], Mia Bryttings[15], Itziar Casado[3,4], Amparo Larrauri[4,5], Josephine-L K Murray[6], Sylvie Behillil[16,17], Brechje de Gier[8], Ivan Mlinarić[9], Joan O'Donnell[10], Ana Paula Rodrigues[11], Ruby Tsang[12,13], Olivia Timnea[14], Marit de Lange[8], Maximilian Riess[15], Jesús Castilla[3,4], Francisco Pozo[16], Mark Hamilton[6], Alessandra Falchi[19], Mirjam J Knol[8], Sanja Kurečić Filipović[9], Linda Dunford[20], Raquel Guiomar[11], Jade Cogdale[21], Carmen Cherciu[14], Tessa Jansen[2], Theresa Enkirch[15], Luca Basile[4,22], Jeff Connell[20], Verónica Gomez[11], Virginia Sandonis Martín[18], Sabrina Bacci[23], Angela MC Rose[1], Lucia Pastore Celentano[23], Marta Valenciano[1], I-MOVE-COVID-19 and ECDC primary care study teams[24]



RAPID COMMUNICATION

Effectiveness of the adapted bivalent mRNA COVID-19 vaccines against hospitalisation in individuals aged ≥ 60 years during the Omicron XBB lineage-predominant period: VEBIS SARI VE network, Europe, February to August, 2023

Liliana Antunes[1], Clara Mazagatos[2,3], Iván Martínez-Baz[4,5], Verónica Gomez[6], Maria-Louise Borg[7], Goranka Petrović[8], Róisín Duffy[9], François E Dufrasne[10], Ralf Dürrwald[11], Mihaela Lazar[12], Ligita Jancoriene[13], Beatrix Oroszi[14], Petr Husa[15], Jennifer Howard[1], Aryse Melo[16], Francisco Pozo[17], Gloria Pérez-Gimeno[2,3], Jesús Castilla[4,5], Ausenda Machado[6], Aušra Džiugytė[7], Svjetlana Karabuva[18], Margaret Fitzgerald[9], Sébastien Fierens[19], Kristin Tolksdorf[20], Silvia-Odette Popovici[21], Auksė Mickienė[22], Gergő Túri[14], Lenka Součková[15], Nathalie Nicolay[23], Angela MC Rose[1], on behalf of the European Hospital Vaccine Effectiveness Group[24]

Immunological imprinting (influenza)

- Immunological imprinting by first childhood influenza infection → future birth cohort differences in vaccine effectiveness
- First addressed in 2015–16, again in 2018–19, now in 2023–24

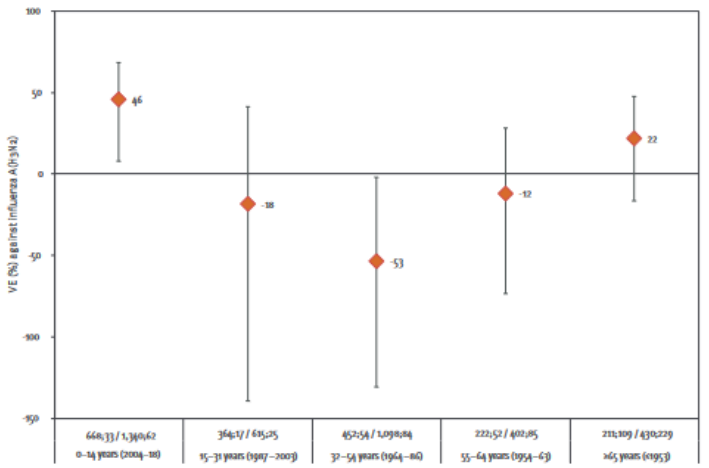
RESEARCH

Low 2018/19 vaccine effectiveness against influenza A(H3N2) among 15–64-year-olds in Europe: exploration by birth cohort

Esther Kissling[1], Francisco Pozo[2], Silke Buda[3], Ana-Maria Vilcu[4], Alin Gherasim[5,6], Mia Brytting[7], Lisa Domegan[8,9], Verónica Gómez[10], Adam Meijer[11], Mihaela Lazar[12], Vesna Višekruna Vučina[13], Ralf Dürrwald[14], Sylvie van der Werf[15,16], Amparo Larrauri[5,6], Theresa Enkirch[7], Joan O'Donnell[8], Raquel Guiomar[17], Mariëtte Hooiveld[18], Goranka Petrović[13], Elena Stoian[12], Pasi Penttinen[19], Marta Valenciano[1], I-MOVE primary care study team[20]

FIGURE 2

Birth cohort-specific vaccine effectiveness against influenza A(H3N2), I-MOVE primary care multicentre study, Europe, influenza season 2018/19 (n = 5,802)



VE: vaccine effectiveness.

Numbers on the x axis represent: cases; vaccinated cases / controls; vaccinated controls.

- SARS-CoV-2 immunological imprinting also relevant

Clade and variant-specific VE

- **(Sub)clade-specific influenza VE** from 2015
- Important granularity to better understand vaccine performance in the context of several circulating clades
- Linking epi and genetic sequencing data at individual level
  - Results weighted by sampling fraction
  - Further granularity: VE by mutation at key positions within the hemagglutinin
  - Helps understand which amino acid substitutions are key for immune escape

- Variant-specific COVID-19 VE from 2021
  - Using variant-predominant periods
  - Linking epi and study genetic sequencing data (primary care)


Contents lists available at ScienceDirect

Vaccine: X

journal homepage: www.elsevier.com/locate/jvacx

Effectiveness of influenza vaccine against influenza A in Europe in seasons of different A(H1N1)pdm09 and the same A(H3N2) vaccine components (2016–17 and 2017–18)

Esther Kissling [a,*], Francisco Pozo [b], Silke Buda [c], Ana-Maria Vilcu [d], Caterina Rizzo [e,f], Alin Gherasim [g,h], Judit Krisztina Horváth [i], Mia Brytting [j], Lisa Domegan [k], Adam Meijer [l], Iwona Paradowska-Stankiewicz [m], Ausenda Machado [n], Vesna Višekruna Vučina [o], Mihaela Lazar [p], Kari Johansen [q], Ralf Dürrwald [r], Sylvie van der Werf [s,t], Antonino Bella [e], Amparo Larrauri [g,h], Annamária Ferenczi [i], Katherina Zakikhany [j], Joan O'Donnell [k], Frederika Dijkstra [l], Joanna Bogusz [m], Raquel Guiomar [u], Sanja Kurečić Filipović [o], Daniela Pitigoi [v], Pasi Penttinen [q], Marta Valenciano [a], I-MOVE/I-MOVE+ study team [1]

Other topics of interest

- VE against outcomes of different severity
  - from VE against asymptomatic outcome to against death
- Vaccine type/platform-specific VE
- Effect of repeated vaccination
- Vaccination strategy that provides optimal protection
  - incl. co-administration of vaccines
- Hybrid immunity – VE effect modification by previous SARS-CoV-2 infection
- Vaccine programme impact
  - Severe outcomes averted
  - Indirect protection

- Well-designed studies, replicated across study groups, international discussions/sharing → Will help understand key topics/study questions

Challenges and next steps

Challenges

- Sustainability of multicentre study funding and teams (human resources), and access to electronic health record linkage during inter-pandemic phases
- Robustness of multicentre studies during emergency and crisis phases
- Anticipate the most relevant research questions during interpandemic and pandemic phases
- Geographical diversity of vaccines used, vaccine coverage and epidemiology of respiratory infections
- Inclusion of serological results in analyses
- Validity of outcome and vaccination variables/sources
- Heterogeneity between study sites' master protocol implementation
- Internal validity issues: possible confounding, selection and classification biases

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Evaluation studies

Challenges

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Evaluation studies

Additional studies around control selection, self-testing in the general popuation

Summary

- VEBIS platform provides important resource to monitor vaccine effectiveness
  - Pooling studies increases sample sizes and precision to answer key questions
  - Informs key public health decisions and can address different questions
  - Catalyses technical capacity in EU/EEA and beyond
  - Depends on efforts of many
- Lessons learnt for other vaccine preventable diseases
  - Nest VE studies under systematic data collection for surveillance (sentinel, non-sentinel, EHR)
    - Using robust generic protocols
    - Collection of vaccine uptake data
    - Collection of other variables needed for adjustment, stratification, research questions
- Continuing vaccine effectiveness studies essential to inform:
  - Public health policy decisions
  - Research questions for vaccines and vaccination programmes

Acknowledgements

- **VEBIS consortium partner leads**
  - **Instituto de Salud Carlos III (Spain):** Amparo Larrauri, Clara Mazagatos, Gloria Perez Gimeno, Paco Pozo
  - **Instituto de Salud Publica y Laboral Navarre (Spain):** Jesus Castilla, Ivan Martínez-Baz, Itziar Casado Buesa
  - **Instituto de Salud Instituto Nacional de Saúde Doutor Ricardo Jorge (Portugal):** Ausenda Machado, Vania Gaio, Ana Paula Rodrigues, Raquel Guiomar, Aryse Melo
  - **Health Protection Surveillance Centre (Ireland):** Joan O'Donnell, Lisa Domegan
- **VEBIS scientific project leads**
  - **Primary care:** Esther Kissling, Charlotte Laniece Delaunay, Marine Maurel (Epiconcept)
  - **Hospital:** Angie Rose, Liliana Antunes, Jenny Howard (Epiconcept)
  - **Electronic Health Registers:** Baltazar Nunes, James Humphreys, Esther Kissling, Anthony Nardone (Epiconcept); Susana Monge (Instituto de Salud Carlos III)
  - **Healthcare workers:** Camelia Savulescu, Albert Prats Uribe, Madelyn Rojas, Ranya Mulchandani, Anthony Nardone (Epiconcept)
- **ECDC:** Sabrina Bacci, Kim Brolin, Nathalie Nicolay, Marlena Kaczmarek, Kate Olsson
- **Epiconcept:** Alexis Sentis, Alain Moren, Valerie Nancey
- **All partner institutes/hospitals**

Thank you for your attention

Questions?