

**Use of validation
results in studies**

*Validation in BIFAP
and application in
studies: experience
and challenges*

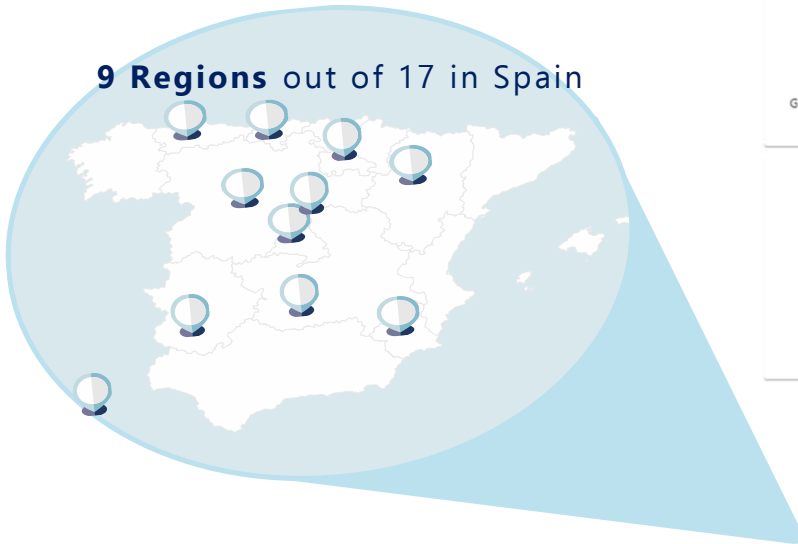


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**Division of Pharmacoepidemiology and
Pharmacovigilance , AEMPS**



Base de datos para la Investigación Farmacoepidemiológica en el **Ámbito Público**

9 Regions out of 17 in Spain



Data for Public Health and Drug Safety

BIFAP includes information provided by general practitioners and primary care paediatricians from the National Health System.



From **2001**, anual update

Link to hospital discharge diagnosis and SARS-CoV-2 test results

Importance of Data Validation in BIFA



We are aware of the possibility of bias from outcome misclassification due to

- Imprecise algorithms;
- Recording of presumed diagnoses by the GP
- Research on outcomes diagnosed in secondary healthcare (ex. Fractures require MRI to confirm)
- ...

Bone
Volume 190, January 2025, 117325

Full Length Article

Multiple vertebral fractures after antiosteoporotic medications discontinued: A comparative study to evaluate the denosumab

ORIGINAL REPORT | WILEY

Mar Martín-Pérez¹, Sergio López-Álvarez², Elisa Martín-Merino³, Mar Martín-Pérez⁴, Dolores Montero-Corominas⁵

The recording and prevalence of Inflammatory bowel disease in girls' primary care medical Spanish records

Abstract
Purpose: Inflammatory bowel disease (IBD) recording validation among girls in the Spanish Primary Care Database For Pharmacokinological Research (BIFA).
Methods: In this observational study, girls aged 9 to 18 years registered in BIFA between 2002 and 2016, were followed up until there was a recorded IBD diagnosis or until they were 18 years old. A retrospective analysis was performed to evaluate the recording and prevalence of IBD in girls' primary care medical Spanish records.
DOI: 10.4274/jerpe.galenos.2020.0225
J Clin Res Pediatr Endocrinol 2021;13(2):170-175

ORIGINAL ARTICLE

An Estimation of the Incidence of Thyroiditis Among Girls in Primary Care in Spain

Elisa Martín-Merino¹, Aida Moreno-Juste², Belén Castillo Cano¹, Mar Martín Pérez¹, Dolores Montero Corominas¹

¹Spanish Agency for Medicines and Medical Devices (AEMPS), Department of Medicines for Human Use, Pharmacoepidemiology and Pharmacovigilance Unit, Madrid, Spain
²Servicio Aragón de Salud (SAS), EpíCron Research Group, Aragón Health Sciences Institute (IACS), IIS Aragón; Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC), Zaragoza, Spain

We **measure** outcome misclassification on most studies
(**True positives** by manual review of clinical histories)

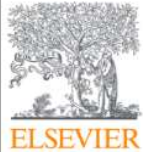
We usually **correct the estimates** (OR or HR) for outcome misclassification by **restricting** the analysis to confirmed cases (in main or secondary analysis; to spot differences)

Identify precise cases in BIFAP



Manual review of patients' eHR

CM	11/10/2021	54150009	CVA (CATARRO VIAS ALTAS) del 11/10/2021			
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			3 VOMITOS ALIMENTARIOS DESDE ESTA MA?ANA. NO DIARREA. EC. BAG. ACP: NORMAL. ORL NORMAL. ABDOMEN BLANDO Y DEPRESIBLE, SIN MASAS NI HEM. MANIOBRAS APENDICULARES NEGATIVAS. BIEN HIDRATADO. TTO PROBAR CON TOLERANCIA ORAL CON SUERORAL HIPOS?DICO, DIETA BLANDA, ULTRALEVURA. SI EMPEORA Y/O NO MEJORA, VOLVER A CONSULTAR.			
RE	03/11/2021	946582	A03FA03	""	N_REC. 1(1)	7(0)
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CM	20/04/2022	28743005	TOS, EXPECTORACION (AG./CRO.) del 08/11/2011			
			DESDE AYER PRESAENTA MALESTAR GENERAL. TOS. DECIMAS Y UN VOMITO. ACTUALMENTE BEG. AFEBRIL (37.1) POCO OUEIUMBROSOS. OTOSCOPIA LIMPIA. GARGANTA HIP?			

Identify precise cases in BIFAP









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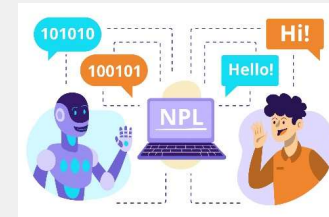


Full Length Article

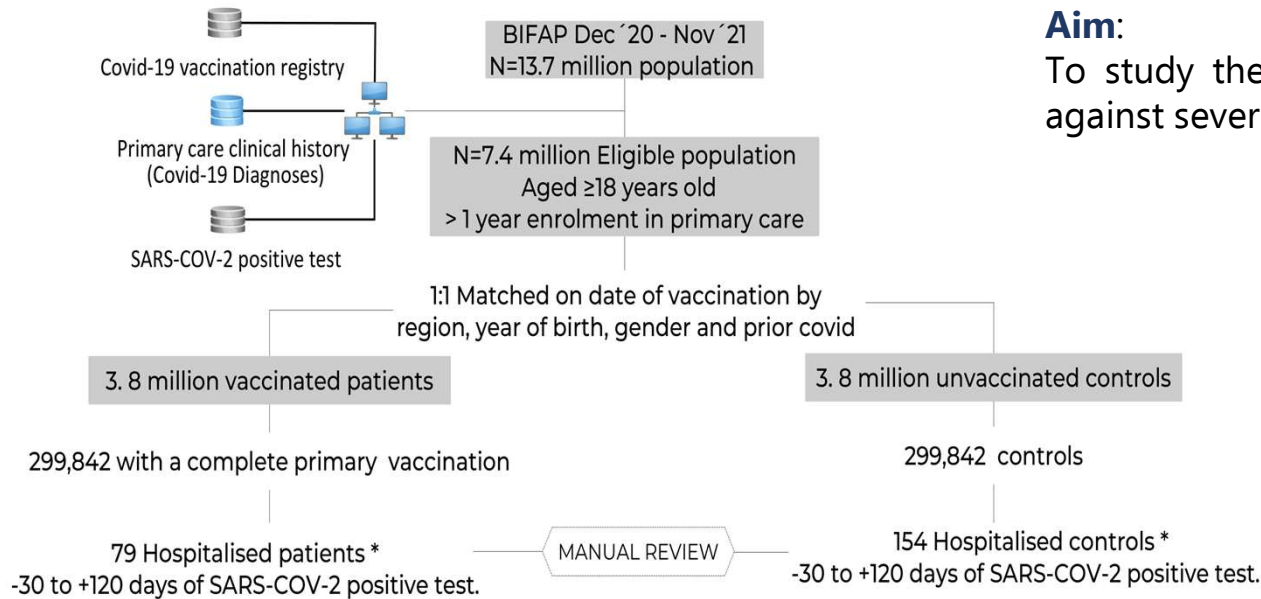
Multiple vertebral fractures after antiosteoporotic medications discontinuation: A comparative study to evaluate the potential rebound effect of denosumab

Mar Martín-Pérez ^a  , Beatriz Sánchez-Delgado ^{a,1} , Patricia García-Poza ^a , Sergio López-Álvarez ^b , Elisa Martín-Merino ^a 

Natural Language Processing (NLP) algorithms



Case Study – Hospitalization ‘for’ Covid-19 algorithm



Aim:

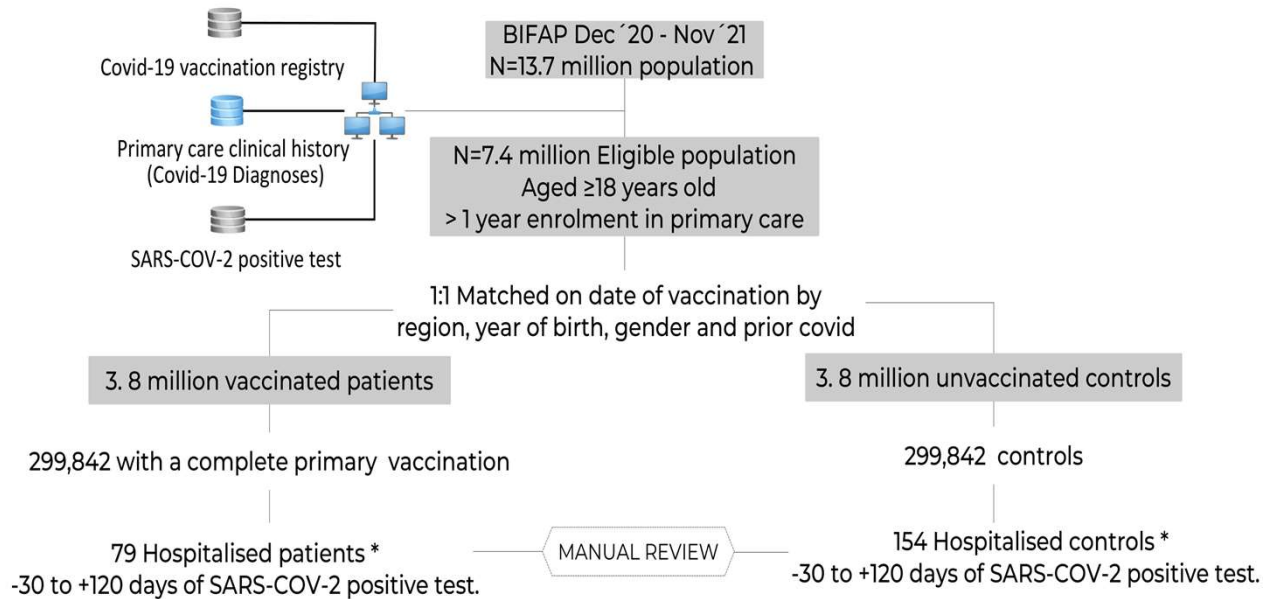
To study the effectiveness of COVID-19 vaccines against severe Covid-19.

The primary **reason for hospital admission** was not available

Algorithm: hospitalizations 'with' COVID-19, SARS-CoV-2 infection, or pneumonia

Vaccine effectiveness (VE) could be under- or overestimated if the misclassification were differential.

Case Study – Hospitalization ‘for’ Covid-19 algorithm



Validation objective

- To assess whether COVID-19 was the main reason for hospitalization
- If not, to assess what the misclassification was among vaccinated people and controls

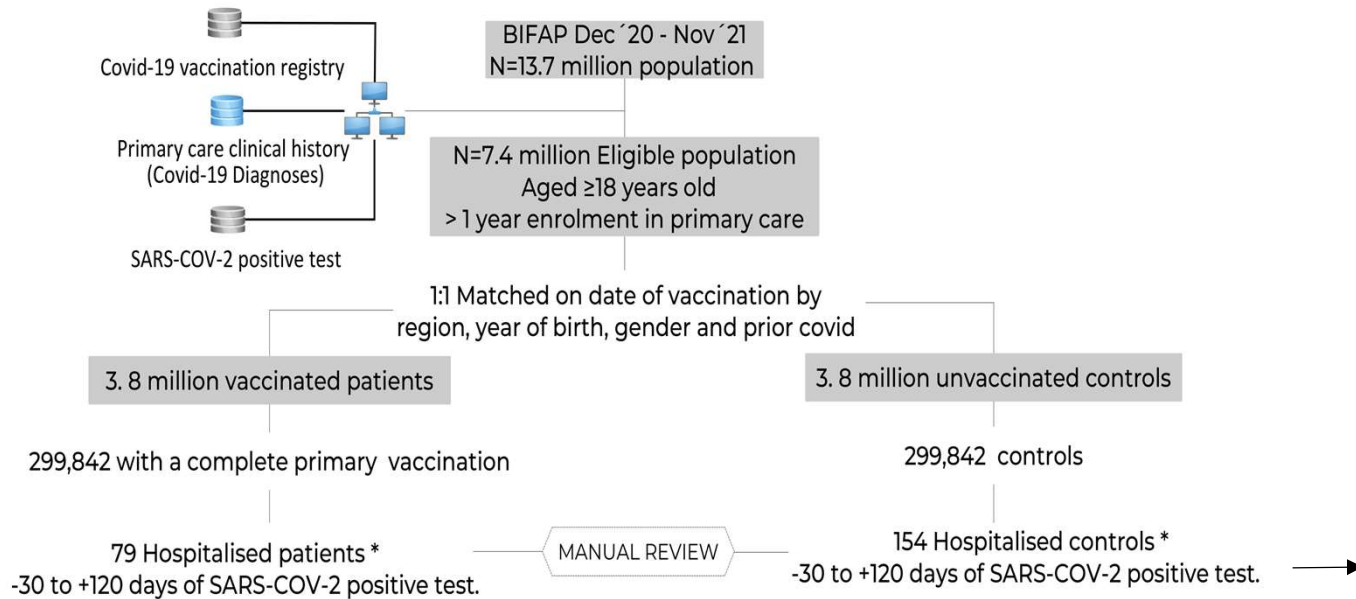


Validation method:

A manual review of patient clinical notes blinded to the vaccination status of

1. A sample size → PPV
2. Total cases (since **no formula to correct HR by PPV**)

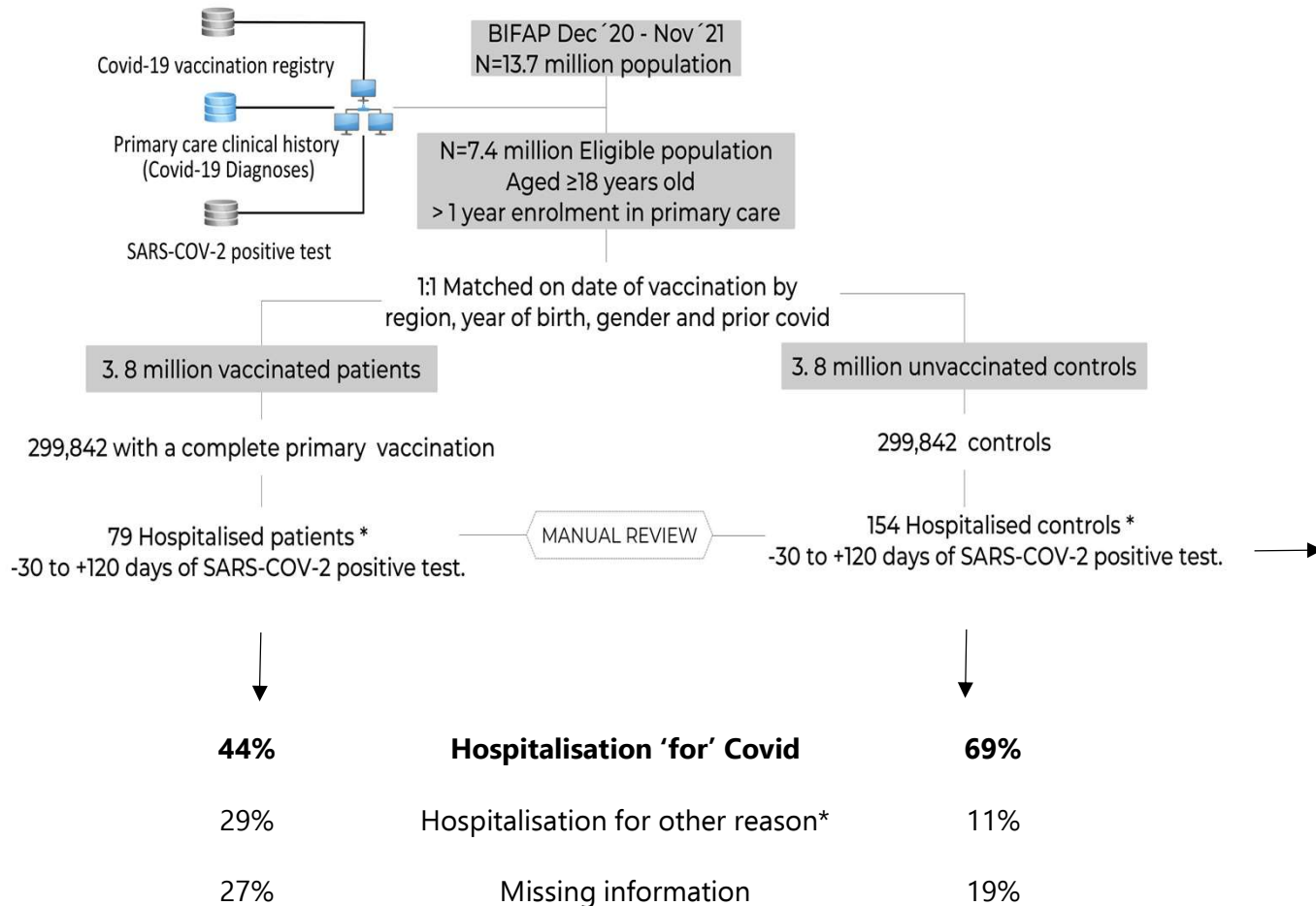
Case Study – Hospitalization ‘for’ Covid-19 algorithm



VE before correction

- MD = 74% (16-92%)
- JA = 4% (-63% to 44%)
- PF = 79% (95% CI: 68-87%)
- AZ = 92% (43-99%).

Case Study – Hospitalization ‘for’ Covid-19 algorithm



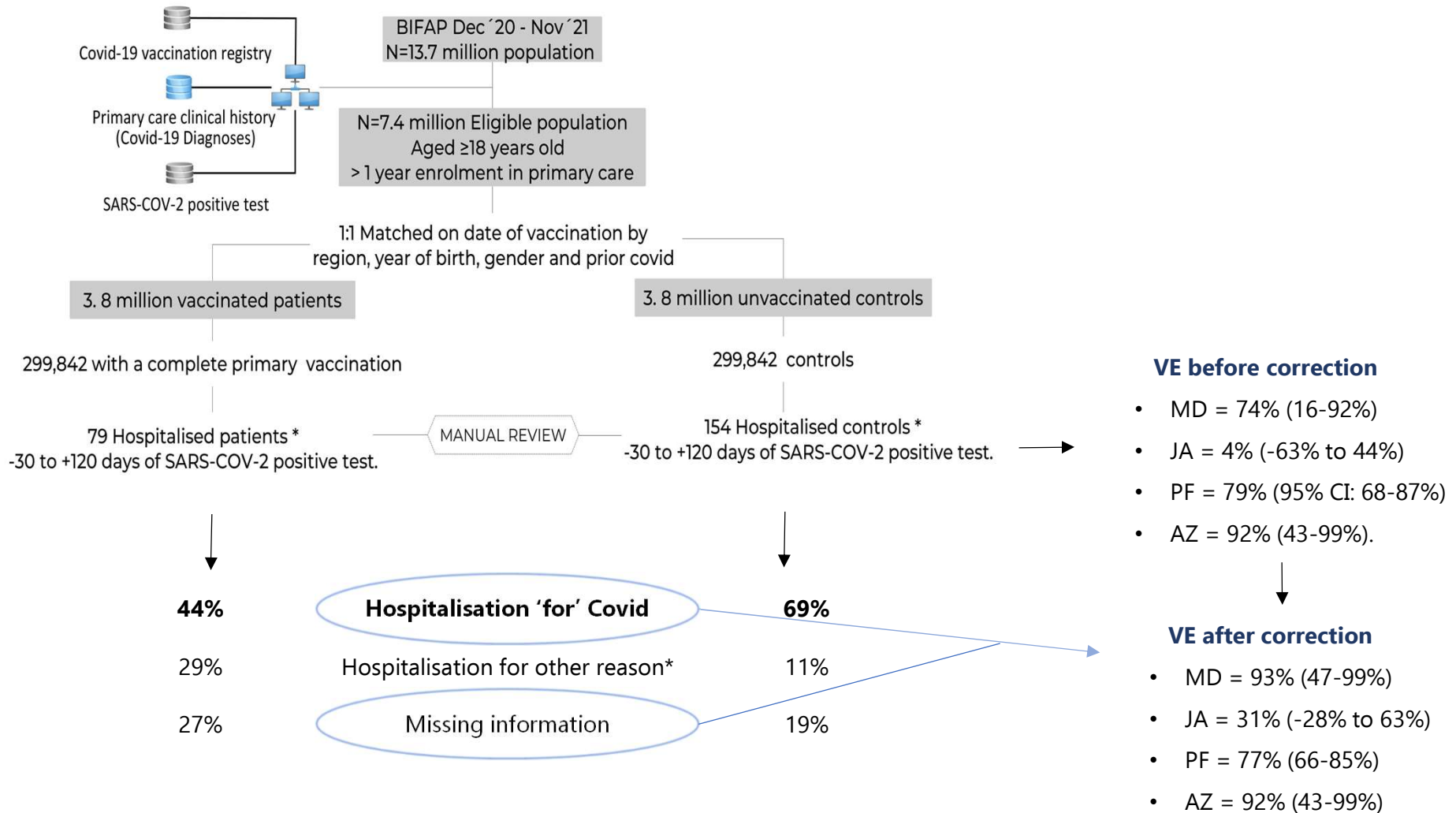
VE before correction

- MD = 74% (16-92%)
- JA = 4% (-63% to 44%)
- PF = 79% (95% CI: 68-87%)
- AZ = 92% (43-99%).

Misclassification of the Covid-19 severity was **differential** between vaccinated and controls.

Missing information suggesting **differential** recording and/or medical assistance.

Case Study – Hospitalization ‘for’ Covid-19 algorithm



How can we adjust the VE (1-HR) using the PPV derived from a different study?



Manual review and PPV estimation of hospitalization 'with' COVID-19 in people aged 12-18 years

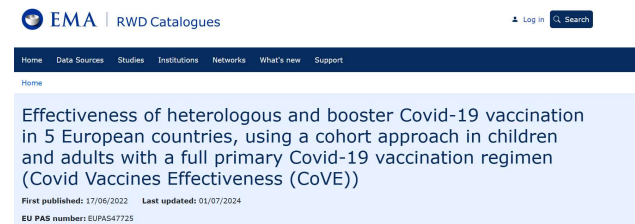
Application to an effectiveness study



758. VALIDACIÓN DE LA INFORMACIÓN SOBRE COVID-19 GRAVE EN NIÑOS Y ADOLESCENTES REGISTRADOS EN BIFAP

B. Sánchez Delgado, M. Martín Pérez, B. Castillo Cano, E. Martín Merino

Agencia Española de Medicamentos y Productos Sanitarios (AEMPS).



PPV non-vaccinated = 63%
PPV vaccinated = 24%

Removing % of automatic cases expected to be false positives

Adolescents

VE crude = 34%

2) Correction of VE

VE crude = 75%

- How can we adjust the VE (1-HR) using the PPV derived from a different study?



<https://apps.p-95.com/app/ispe> corrects RR according to PPV and Sensitivity

- Is there any method available to adjust the HR by PPV?



Request/Recommendations

Requests for Professors Ersilia and Robert

- Statistical methods for adjusting HR by PPV
- Provide guidance on handling imprecise PPV and frequent missing information in the available 'gold-standard'

Recommendations for the investigator who is writing a protocol (Xabi):

- Estimate PPV/other validation parameters by exposure categories to detect differential misclassification and correct the estimates accordingly (even in Target Trial Emulations)
- Plan for building re-usable NLP/AI algorithms

Thank you

AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS

