PASS Interim Report 1

Active substance	AZD1222
Product number	EMEA/H/C/005675
Version number	1.0
Date	21 April 2022

Post-Authorisation Safety Study of AZD1222

A post-authorisation/post-marketing observational study to evaluate the association between exposure to AZD1222 and safety concerns using existing secondary health data sources

[redacted]

Marketing Authorisation Holder(s)

Marketing authorisation holder(s)	***AstraZeneca AB*** *151 36 Södertälje, Sweden*
MAH contact person	[redacted] AstraZeneca AB 151 85 Södertälje Sweden

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Approved by:

[redacted]

Cristina Rebordosa, MD, PhD
Director, Epidemiology
RTI Health Solutions

Date

Approved by:

PASS INFORMATION

Title	A post-authorisation/post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to AZD1222 and safety concerns
Version identifier of the interim study report 1	1.0
Date of last version of the final study report	21 April 2022
EU PAS register number	EUPAS43556
Active substance	ChAdOx1-S [recombinant] (AZD1222) (formerly ChAdOx1 nCoV-19)
Medicinal product	Vaxzevria
Product number	EMEA/H/C/005675
Procedure number	EMEA/H/C/005675/MEA/007
Marketing authorisation holder(s)	AstraZeneca AB
Joint PASS	No
Research question and objectives	Interim Report 1: To describe the incidence rates of the adverse events of special interest and to describe the timing and type of second dose of any COVID-19 vaccine (AZD1222 or other) over the study period among subjects having received a first dose of AZD1222
Country (-ies) of study	Italy, the Netherlands, Spain, and United Kingdom

Author	Cristina Rebordosa, MD, PhD RTI Health Solutions Av. Diagonal 605, 9-1 08028 Barcelona SPAIN Telephone: +34.93.362.2807 Email: crebordosa@rti.org [redacted] Telephone: [redacted] Email: [redacted] On behalf of the AZD1222 PASS research team

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1. ABSTRACT

Title

A post-authorisation/post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to AZD1222 and safety concerns

Keywords

AZD1222; safety concerns; COVID-19

Rationale and Background

AZD1222 is a vaccine developed to prevent COVID-19 that received emergency use authorisation in the United Kingdom (UK) on 30 December 2020 and was granted conditional marketing authorisation by the European Commission on 29 January 2021. As part of the marketing authorisation, AstraZeneca AB (AZ) was asked to conduct a post-authorisation safety study (PASS) to examine the safety of AZD1222. The protocol (version 3.0 dated 7 July 2021) was endorsed by the European Medicines Agency (EMA) on 22 July 2021, and by the Medicines and Healthcare products Regulatory Agency (MHRA) (version 2.0 dated 14 June 2021) on 9 July 2021.

This interim report 1 presents the results of interim analysis 1 focused on the description of the patterns of vaccination and the incidence of the adverse events of special interest (AESIs).

Research Question and Objectives

1 To describe the incidence rates (IRs), prevalence proportion (PP), or cumulative incidence (1 – Kaplan-Meier [KM] estimator) of prespecified AESIs in subjects who received at least 1 dose of AZD1222 (either as first or subsequent dose), in matched cohorts of subjects who received AZD1222 as the first dose, and in subjects who had not yet received any COVID-19 vaccine (unvaccinated subjects).

2 To describe the timing and type of second dose of any COVID-19 vaccine (AZD1222 or other) over the study period among subjects who received AZD1222 as the first dose.

Study Design

A multinational, retrospective cohort study describing the occurrence of AESIs was conducted in subjects who received at least 1 dose of AZD1222, and in the matched cohorts of subjects who received AZD1222 as a first dose and unvaccinated subjects.

Setting

This study, which is conducted in the VAC4EU (Vaccine Monitoring Collaboration for Europe, https://vac4eu.org/) research environment, uses a common protocol across all study sites, a common data model (CDM), and common analytics. The study is conducted using

information collected in secondary automated electronic healthcare data sources in Europe. The data sources are the Clinical Practice Research Datalink (CPRD) in the UK, the Valencia Health System Integrated Database (VID) (data not included in interim report 1), the Information System for Research in Primary Care (SIDIAP) database in Spain, the Regional Health Agency of Tuscany (ARS Toscana) database in Italy, and the PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research in the Netherlands (PHARMO).

The study period for this interim report 1 extends from the introduction of AZD1222 in each country in early 2021 through the latest date of data availability in each data sources, with the latest date among the data sources being 13 October 2021.

Subjects and Study Size, Including Dropouts

The source population for each of the study components comprised all individuals registered in each data source during the study period. The study population included subjects who were exposed to the AZD1222 vaccine and concurrent subjects who had not yet received any COVID-19 vaccine, who served as comparators. Three different populations were identified among subjects exposed to AZD1222: all subjects vaccinated with at least 1 dose of AZD1222 during the study period without applying any other inclusion and exclusion criteria (*all vaccinated population*); a subset of the all vaccinated population including only those subjects that received AZD1222 as their first COVID-19 vaccine dose (*all vaccinated first dose population*); and all subjects in the all vaccinated first dose population that fulfilled the inclusion and exclusion criteria and were matched to at least 1 unvaccinated subject (*matched population*). Additionally, concurrent unvaccinated subjects, who had not yet received any COVID-19 vaccine, that fulfilled the inclusion and exclusion criteria were included as potentially eligible comparators. Up to 5 unvaccinated subjects that were eligible at the time of the first dose of AZD1222 (index date) of a vaccinated subject were matched by age (± 2 years), sex, geographic region, and prior diagnosis of COVID-19 status to this vaccinated subject. Matching was performed with replacement. The index date of the unvaccinated subjects was assigned as the vaccination date of the matched vaccinated subject. Follow-up for each AESI for each subject started at the beginning of the risk window of dose 1. Follow-up ended on the earliest of the end of the study period, enrolment termination from the health plan or system, death, occurrence of the specific AESI of interest, receiving any COVID-19 vaccine other than AZD1222, the end of the risk window of dose 1 or dose 2 (for AESIs with known risk windows) or until 180 or 365 days after index date (for AESIs with unknown risk window), or receiving AZD1222 (unvaccinated subjects only).

Variables and Data Sources

The exposure of interest was being vaccinated with AZD1222. Other COVID-19 vaccines for were identified for exclusion and censoring purposes. Identification of records for AZD1222 and other COVID-19 vaccines varied by data source.

Safety outcomes included a list of 37 AESIs. These outcomes were identified using algorithms based on codes for diagnoses, and they were defined uniformly across the data sources to the fullest extent possible.

For this interim report 1, only age, sex, geographic region, and prior COVID-19 were defined as covariates. These covariates were used for descriptive and matching purposes.

The following analyses were conducted for each type of AESI: For outcomes with **known risk windows** (those for which the end of the risk window is other than 180 or 365 days, except for anaphylaxis and sudden death), crude IRs and 95% confidence intervals (CIs) were estimated. The crude IR was calculated as the number of subjects with an incident AESI during any of the risk windows for dose 1 or 2 divided by the total person-years accumulated during the risk windows after dose 1 and dose 2 (if it was received) in each cohort. For the vaccinated cohorts, exact 95% CIs were estimated, and for the matched unvaccinated cohort, generalised estimating equation (GEE) models were used to estimate 95% CIs to account for repeated subjects. For anaphylaxis and sudden death, PPs were calculated as number of incident events divided by number of subjects, and exact 95% CIs were estimated. For outcomes with **unknown risk windows** (those with a risk window assigned to end at 180 or 365 days)**,** cumulative incidence was estimated using the 1 − KM estimator at the time of the last subject not censored; 95% CIs were estimated taking into account repeated subjects for the matched unvaccinated cohort.

Results

After applying all eligibility criteria and matching, 4,040,587 vaccinated subjects were included in the AZD1222 matched cohort in CPRD, 558,566 in SIDIAP, 336,792 in ARS Toscana, and 167,087 in PHARMO. In all data sources, more than 95% of the vaccinated subjects were matched on a 1:5 ratio. Most of the unvaccinated subjects were matched fewer than 3 times, although in CPRD, 25% of unvaccinated subjects were matched 5 times or more. Data from VID could not be extracted to be included in interim report 1. Data from VID will be analysed as soon as they become available and results will be shared with the EMA in the next interim report. An evaluation of the actual number of subjects vaccinated with AZD1222 showed that, as of 26 September 2021, VID contained data on 507,846 subjects who had received at least 1 dose of AZD1222 and 439,613 subjects who had received a second dose (data from the progress report submitted to the EMA on 22 October 2021).

In the *all vaccinated population,* most subjects in CPRD were vaccinated during Q1 2021, whereas in the other data sources, more subjects were vaccinated during Q2 2021. Subjects in CPRD were younger than subjects in the other data sources. In all data sources, there was a slightly higher proportion of females than males.

The duration of follow-up among subjects in the unvaccinated cohort (median duration less than 2 months in all data sources) was shorter than among subjects in the AZD1222 cohort (median follow-up ranged from 7.1 months in CPRD to 2.3 months in PHARMO). The most frequent reasons for censoring follow-up differed between the AZD1222 cohort (ie, end of study period) and the unvaccinated cohort (ie, receiving a COVID-19 vaccine, either AZD1222 or other).

Most subjects in CPRD and ARS Toscana who received AZD1222 as the first dose received a second dose of any COVID-19 vaccine. In SIDIAP and PHARMO, with shorter study periods, 54.45% and 27.76% of subjects, respectively, received a second dose of any COVID-19 vaccine. In all data sources, more than 92% of those second-dose vaccines were AZD1222, and most vaccinated subjects received the second dose between 9 and 12 weeks after the first dose.

Some AESIs could not be evaluated due to lack of specific codes to identify the events in some coding systems, and some AESIs had very few or no events. Risk estimates (IR, PP, and cumulative incidence) obtained for the *all vaccinated population* were almost identical to those observed for the matched vaccinated population. The IR (95% CI) per 10,000 person-years of thrombosis with thrombocytopaenia syndrome (TTS) ranged from 0.17 (0.09-0.28) to 0.67 (0.22-1.56) among subjects in the AZD1222 matched cohort and from 0.01 (0.00-0.04) to 0.37 (0.10-1.35) among subjects in the unvaccinated cohort, except in PHARMO where no events were identified. The IR (95% CI) per 10,000 person-years of thrombosis without thrombocytopaenia ranged from 0.13 (0.00-0.75) to 0.28 (0.03-1.02) among subjects in the AZD1222 cohorts and from 0.08 (0.02-0.32) to 0.21 (0.03-1.52) among subjects in the unvaccinated cohorts; no events were identified in PHARMO. The IR (95% CI) per 10,000 person-years of thrombosis with associated bleeding ranged from 0.07 (0.02-0.15) to 0.67 (0.22-1.56) among subjects in the AZD1222 cohorts and from 0.01 (0.00-0.04) to 0.53 (0.19-1.51) among subjects in the unvaccinated cohorts; no events were identified in PHARMO. The IR (95% CI) per 10,000 person-years of thrombocytopaenia ranged from 1.56 (0.78-2.78) to 15.81 (13.08-18.93) among subjects in the AZD1222 matched cohorts and from 1.74 (0.66-4.56) to 22.18 (18.52-26.55) among subjects in the unvaccinated cohorts. The other AESI with the largest numerical differences between vaccinated and unvaccinated subjects were anaphylaxis and stress cardiomyopathy. However, this was not consistent across all data sources. The PP (95% CI) per 10,000 subjects of anaphylaxis ranged from 0.06 (0.01-0.21) to 2.34 (1.67-3.20) among subjects in the AZD1222 matched cohorts and from 0.03 (0.01-0.05) to 1.06 (0.84-1.30) among subjects in the unvaccinated matched cohorts; no events were identified in ARS Toscana. The IRs (95% CI) per 10,000 person-years of stress cardiomyopathy ranged from 0.49 (0.36-0.66) to 0.80 (0.29-1.75) among subjects in the AZD1222 matched cohorts and from 0.13 (0.02-0.95) to 0.80 (0.43-1.50) among subjects in the unvaccinated matched cohort; no events were identified among subjects in the AZD1222 matched cohort in PHARMO.

Discussion

Results from interim analysis 1 are descriptive. Overall, in Spain, Italy, Netherlands, and the UK, more than 5.2 million subjects were vaccinated with AZD1222, and 22.5 million available unvaccinated comparators could be matched. Among subjects who received a first dose of AZD1222, when a second dose was also observed, this was most frequently also AZD1222. Vaccine coverage and distribution was in line with national and regional data.

Duration of follow-up was short among both cohorts but especially among the unvaccinated cohort. This may limit the evaluation of AESIs with unknown risk window, which require longer durations of follow-up. An evaluation of the availability of active comparators will be included in interim report 2.

The crude incidences of the AESIs varied by data source. This can be attributed to differences in the type of data available and in the granularity of the coding systems, rather than to true differences in the incidence of these AESIs between countries. The incidence of some AESIs was higher among vaccinated than among unvaccinated subjects, and the largest numerical difference occurred for the incidence of TTS, thrombocytopaenia with bleeding, anaphylaxis, and stress cardiomyopathy, but this was not consistent across all data sources. Differences in the incidence of AESIs between vaccinated and unvaccinated subjects in this report should be interpreted with caution given the short study period included in this first data extraction and the lack of standardisation or adjustment for potential confounders and potential differences in the baseline characteristics of the study cohorts, which is planned for future analyses.

Marketing Authorisation Holder(s)

AstraZeneca AB
151 36 Södertälje, Sweden

Names and Affiliations of Principal Investigators

Cristina Rebordosa, MD, PhD
Director, Epidemiology
RTI Health Solutions
Av. Diagonal 605, 9-1
08028 Barcelona SPAIN

2. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ABUCASIS	Ambulatory Medical Record in VID
ACCESS	Vaccine COVID-19 Monitoring Readiness
ADEM	Acute Disseminated Encephalomyelitis
AED	Accident and Emergency Department
AESI	Adverse Event of Special Interest
ARDS	Acute Respiratory Distress Syndrome
ARS Toscana	Regional Health Agency of Tuscany [Agenzia Regionale di Sanità Della Toscana]
ATC	Anatomical Therapeutic Chemical
AZ	AstraZeneca
AZD1222	AstraZeneca COVID-19 vaccine (Vaxzevria® in Europe)
CDM	Common Data Model
CHESS	COVID-19 Hospitalisation in England Surveillance System
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CPRD	Clinical Practice Research Datalink
CPRD GOLD	General Practitioner Online Database of CPRD
CVST	Cerebral Venous Sinus Thrombosis
DAP	Database Access Partner
DRE	Digital Research Environment
DSRU	Drug Safety Research Unit
DVT	Deep Vein Thrombosis
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ETL	Extraction, Transformation, and Loading
EU	European Union
FAIR	Findable, Accessible, Interoperable, and Reusable
FDA	Food and Drug Administration
FISABIO	Foundation for the Promotion of Health and Biomedical Research of Valencia Region
FU	Follow-up
GAIA	Pharmaceutical Module in VID
GBS	Guillain-Barré Syndrome

Abbreviation or special term	Explanation
GEE	Generalised Estimating Equation
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practices
HES	Hospital Episodes Statistics
ICD-9	International Classification of Diseases, Ninth Revision
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10	International Classification of Diseases, 10th Revision
ICD-10-ES	International Classification of Diseases, 10th Revision, Spanish Edition
ICMJE	International Committee of Medical Journal Editors
ICNARC	Intensive Care National Audit and Research Centre
ICPC	International Classification of Primary Care
IDIAP Jordi Gol	Institute of Research in Primary Care [Institut Universitari D'Investigació en Atenció Primària Jordi Gol]
IOM	Institute of Medicine
IR	Incidence Rate
ISPE	International Society for Pharmacoepidemiology
KM	Kaplan-Meier
MAH	Marketing Authorisation Holder
MBDS	Minimum Basic Data Set at Hospital Discharge
ME	Myalgic Encephalitis
MHRA	Medicines and Healthcare products Regulatory Agency
MIS	Multisystem Inflammatory Syndrome
mRNA	Messenger Ribonucleic Acid
NA	Not Available
NHS	National Health Service
NIHR	National Institute for Health Research
NR	Not Reported
OMOP	Observational Medical Outcomes Partnership
ORION	Hospital Medical Record in VID
PASS	Post-Authorisation Safety Study
PCR	Polymerase Chain Reaction
PHARMO	PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research (the Netherlands)
PHE	Public Health England
PP	Prevalence Proportion
PVFS	Postviral Fatigue Syndrome

Abbreviation or special term	Explanation
PY	Person-Years
Q1, Q3	First and Third Quartiles
QC	Quality Control
RMP	Risk Management Plan
RTI-HS	RTI Health Solutions
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Statistical Analysis System
SCRI	Self-controlled Risk Interval
SD	Standard Deviation
SGSS	Second Generation Surveillance System (PHE)
SIA	Ambulatory Information System (VID)
SIDIAP	Information System for Research in Primary Care [Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària] (Spain)
SIP	Population Information System (VID)
TP	Thrombocytopaenia
TTS	Thrombosis With Thrombocytopaenia Syndrome
UMCU	University Medical Center Utrecht
UK	United Kingdom
VAC4EU	Vaccine Monitoring Collaboration for Europe
VAED	Vaccine-Associated Enhanced Disease
VID	Valencia Health System Integrated Database (Spain)
VIS	Vaccine Information System
VTE	Venous Thromboembolism

3. INVESTIGATORS

AstraZeneca Responsible Parties

Role	Name, title, qualifications
Scientific lead, epidemiology	[redacted]
Operational lead	[redacted]
Study physician	[redacted]
Statistician	[redacted]
Pharmacovigilance	[redacted]
Data Management	[redacted]
Statistician	[redacted]
Pharmacovigilance	[redacted]

Collaborating institutions

Institution name	Role	Name, title, qualifications
RTI Health Solutions (RTI-HS)	Principal Investigator	Cristina Rebordosa, MD, PhD Director Epidemiology
	Co-Principal Investigator	[redacted]
	Senior Adviser	[redacted]
	Senior Adviser	[redacted]
	Statistician	[redacted]
	Statistician	[redacted]
Drug Safety Research Unit (DSRU)	Principal Investigator	[redacted]
	Pharmacoepidemiologist	[redacted]
	Epidemiologist	[redacted]
	Epidemiologist	[redacted]
The Foundation for the Promotion of Health and Biomedical Research of Valencia Region, (FISABIO)	Project Lead	[redacted]
	Project Statistician	[redacted]
	Project Statistician	[redacted]
	Project Statistician	[redacted]
	Pharmacovigilance	[redacted]
	Epidemiologist	[redacted]
	Project Manager	[redacted]

Institution name	Role	Name, title, qualifications
Agenzia Regionale di Sanità Della Toscana (ARS Toscana)	Data Scientist, Pharmacoepidemiologist	[redacted]
	Pharmacoepidemiologist	[redacted]
	Data Scientist, Programmer	[redacted]
	Pharmacoepidemiologist	[redacted]
	Pharmacoepidemiologist	[redacted]
Research Institute in Primary Care Jordi Gol (IDIAP)	Principal Investigator	[redacted]
	Pharmacoepidemiologist	[redacted]
	Statistician	[redacted]
	Pharmacoepidemiologist	[redacted]
	Data Scientist	[redacted]
	Investigator	[redacted]
PHARMO Institute	Principal Investigator	[redacted]
	Co-Principal Investigator	[redacted]
	Investigator	[redacted]
	Senior Adviser	[redacted]

Institution name	Role	Name, title, qualifications
University Medical Center Utrecht (UMCU)	Principal Investigator	[redacted]
	Senior Statistician	[redacted]
	Data Engineer/ Epidemiologist	[redacted]
	Data Engineer	[redacted]
	Data Engineer	[redacted]
	Statistician	[redacted]
Vaccine Monitoring Collaboration for Europe (VAC4EU)	VAC4EU Oversight and Support	[redacted]

An independent **scientific advisory board** (SAB) was set up by VAC4EU. The members are Dr. [redacted] and Dr. [redacted]. The SAB reviewed the statistical analysis plan and this interim report 1.

4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Table 1. Milestones

Milestone	Planned date[a]	Actual date
Protocol submission	01 Apr 2021	1 Apr 2021
Protocol endorsement by EMA/MHRA	Jul 2021	9 Jul 2021 (MHRA); 22 Jul 2021 (EMA)
Registration in the EU PAS Register	No later than 6 months after EMA protocol endorsement and before start of data collection	Registered on the 7 Oct 2021 (EUPAS43556)
Statistical Analysis Plan submission	4 months after protocol endorsement (expected November 2021)	Submitted on 30 Nov 2021
Start of data collection[b]	4 months after protocol endorsement (expected November 2021, interim analysis 1)	18 Feb 2022
End of data collection[c]	20-21 months after protocol endorsement (expected March/April 2023, final report)	Planned
Progress report	3 months after protocol endorsement (expected October 2021)	Submitted on 22 Oct 2021
Interim report 1	9 months after protocol endorsement (expected April 2022)	Planned 22 Apr 2022
Interim report 2	15 months after protocol endorsement (expected October 2022)	Planned
Interim report 3	21 months after protocol endorsement (expected April 2023)	Planned
Final report of study results	27 months after protocol endorsement (expected October 2023)	Planned

[a] Start of data collection: the date from which information on the first study subject is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts [IR Art 37(1)]. Simple counts in a database to support the development of the study protocol, eg, to inform the sample size and statistical precision of the study, are not part of this definition.

[b] End of data collection: the date from which the analytical data set is completely available [IR Art 37(2)]. Analytical data set: the minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) of the study.

EMA, European Medicines Agency; EU PAS, European Union electronic Register of Post-Authorisation Studies; MHRA, Medicines and Healthcare products Regulatory Agency.

6. RATIONALE AND BACKGROUND

The novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), the cause of coronavirus disease 2019 (COVID-19), has led to a global pandemic. The AZD1222 vaccine (called Vaxzevria® in Europe) was developed to prevent COVID-19. AZD1222 is a recombinant, replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 spike glycoprotein. Development of AZD1222 was initiated by the University of Oxford with subsequent transfer of development activities to the Sponsor.

On 30 December 2020, the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom (UK) provided authorisation for emergency supply of AZD1222, and on 29 January 2021, the European Commission granted conditional marketing authorisation for the vaccine. AZD1222 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals aged 18 years and older. The primary vaccination course consists of 2 separate intramuscular injections. The second dose should be administered between 4 and 12 weeks (28 to 84 days) after the first dose. However, in all the countries included in this study, to enable as many people to receive the first vaccination as possible before the workforce moved on to administering second doses, or due to shortage issues, the second dose was administered around 10 to 12 weeks (70 to 84 days) after the first dose. A number of restrictions and changes in recommended target populations occurred after the vaccination campaign started in Europe (see Table 2).

Table 2. Restrictions, by Data Source (Country)

CPRD Aurum (UK)[a]	VID (Valencia, Spain)	SIDIAP (Catalonia, Spain)	ARS Toscana (Italy)	PHARMO (Netherlands)
Apr 2021: AZD1222 vaccine not provided to adults under 30 years of age. AZD1222 vaccine not the preferred vaccine for pregnant women of any age who are coming for their first dose May 2021: AZD1222 vaccine not provided to adults under 40 years of age The mRNA-based COVID-19 vaccines are the first choice for a booster dose. However, the AZD1222 vaccine may be used as a booster dose and may be an option for those who cannot receive mRNA-based COVID-19 vaccines	16 Mar 2021: Suspended vaccination with AZD1222 23 Mar 2021: To be used only in individuals aged ≥ 60 years 30 Mar 2021[b]: Restrictions for individuals who are under age 55 years is eliminated 20 Apr 2021[b]: To be used only in subjects aged 60-69 years 11 May 2021[b]: Extended the dose interval up to 16 weeks 22 Jun 2021[b]: Individuals under 60 years of age: Second dose with mRNA vaccine is allowed in individuals who had received the first dose of AZD1222 Individuals 60-69 years of age: Second dose with AZD1222 is allowed	16 Mar 2021: Suspended vaccination with AZD1222 23 Mar 2021: To be used only in subjects aged ≥ 60 years 30 Mar 2021[b]: Restrictions for individuals who are under age 55 years is eliminated 20 Apr 2021[b]: To be used only in subjects aged between 60-69 years. 11 May 2021[b]: Extended the dose interval up to 16 weeks. 21 May 2021: Signed informed consent needed for a second dose of AZD1222 for individuals aged < 60 years 22 Jun 2021[b]: Individuals under 60 years of age: Second dose with mRNA vaccine is allowed in individuals who had received the first dose of AZD1222 Individuals 60-69 years of age: Second dose with AZD1222 is allowed	15-19 Mar 2021: Suspended vaccination with AZD1222[b] 7 Apr 2021: Preferential use in individuals aged > 60 years[b] 11 Jun 2021: To be used only in individuals ≥ 60 years; if individuals were < 60 years and had first dose of AZD1222, an mRNA vaccine should be administered within 8-12 weeks as the second dose 18 Jun 2021: Subjects aged ≥ 60 years who refuse crossing to an mRNA vaccine for the second dose can receive AZD1222 for the second dose 26 Jun 2021: Contraindicated for subjects with history of capillary leak syndrome	14 Mar 2021: Suspended vaccination with AZD1222[b] 18 Mar 2021: Use only in individuals aged 60-64 years and healthcare staff[b] 23 Mar 2021: Use only in individuals aged 60-75 years and healthcare staff[b] 2 Apr 2021: Suspended vaccination with AZD1222[b] 9 Apr 2021: Restarted vaccinations in individuals aged 60-75 years[b]

[a] Additional information regarding the vaccine roll-out programme can be found online: https://www.gov.uk/government/publications/uk-covid-19-vaccines-delivery-plan/uk-covid-19-vaccines-delivery-plan; https://www.gov.uk/government/publications/priority-groups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi-30-december-2020/joint-committee-on-vaccination-and-immunisation-advice-on-priority-groups-for-covid-19-vaccination-30-december-2020#vaccine-priority-groups-advice-on-30-december-2020.

[b] Information at the national level provided by AstraZeneca affiliates.

ARS Toscana, Regional Health Agency of Tuscany; COVID-19, coronavirus disease 2019; CPRD, Clinical Practice Research Datalink; mRNA, messenger ribonucleic acid; PHARMO, PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research; SIDIAP, Information System for Research in Primary Care; UK, United Kingdom; VID, Valencia Health System Integrated Database.

The safety concerns for AZD1222 are based on the European Union (EU) risk management plan (RMP) (EU RMP version 4 succession 2) and include thrombosis with thrombocytopaenia syndrome (TTS); thrombocytopaenia, including immune thrombocytopaenia; Guillain-Barré syndrome; anaphylaxis (important identified risks); thrombosis; nervous system disorders, including immune-mediated neurological conditions; and vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease (important potential risks) [3]. Areas of missing information include use of AZD1222 in pregnant or breastfeeding women, immunocompromised individuals, frail individuals with comorbidities, and individuals with autoimmune or inflammatory disorders; interactions with other vaccines; and long-term safety.

As part of the marketing authorisation, AstraZeneca AB (AZ) was asked to conduct a post-authorisation safety study (PASS) to examine the safety of AZD1222. The protocol (version 3.0 dated 7 July 2021) was endorsed by the European Medicines Agency (EMA) on 22 July 2021 and by the MHRA (version 2.0 dated 14 June 2021) on 9 July 2021. The study was registered in the EU PAS register (EUPAS43556) (https://www.encepp.eu/encepp/viewResource.htm?id=45674) and the protocol posted (https://www.encepp.eu/encepp/openAttachment/fullProtocol/43593).

This report presents the results of interim analysis 1 focused on the incidence rates (IRs) of the adverse events of special interest (AESIs) as defined in the statistical analysis plan (SAP).

7. RESEARCH QUESTION AND OBJECTIVES

The objectives for **interim analysis** 1 were as follows:

3 To describe the IRs of prespecified AESIs in the following groups:
   (a) Subjects who received at least 1 dose of AZD1222 (either as the first or subsequent dose) in the *all vaccinated population*, (see definition of all vaccinated population in Section 9.3.1)
   (b) Subjects who received at least 1 dose of AZD1222 as the first dose in the *matched population* (see definition of *matched population* in Section 9.3.3)
   (c) Subjects who did not receive any vaccination against COVID-19 (unvaccinated subjects) in the *matched population* (see definition of matched population in Section 9.3.3)

4 To describe the timing and type of second dose of any COVID-19 vaccine (AZD1222 or other) over the study period among subjects having received a first dose of AZD1222 (*all vaccinated first dose population*; see definition in Section 9.3.2)

8. AMENDMENTS AND UPDATES

These adjustments were made in the course of study implementation and SAP development and occurred before the start of data collection (see Table 3).

Table 3. Amendments, Updates, and Adjustments

Number	Date	Section of study protocol	Amendment or update	Reason
1	10 Nov 2021	9.1.1	Added matching variables: prior diagnosis of COVID-19 and geographic region	Prior diagnosis of COVID-19 was added to obtain more comparable populations and use study design to address confounding. Geographic region was added to facilitate data extraction in data sources in which converting the whole database into the common data model is an issue due to size
2	10 Nov 2021	9.5.1	CPRD data include only Aurum and not GOLD	Aurum was chosen because it has a larger number of subjects and due to its high percentage of practices with data linkable to hospital and death data, as opposed to CPRD GOLD. This was erroneously stated in the protocol.
3	10 Nov 2021	9.3.2.1	Time window between "thrombosis and thrombocytopaenia for thrombotic thrombocytopaenia syndrome" and "thrombocytopaenia with bleeding" adjusted from 7 to 10 days	To align with VAC4EU COVID-19 vaccine PASS

COVID-19, coronavirus disease 2019; CPRD, Clinical Practice Research Datalink; CPRD GOLD, General Practitioner Online Database of CPRD; PASS, post-authorisation safety study; VAC4EU, Vaccine monitoring Collaboration for Europe.

9. RESEARCH METHODS

9.1 Study Design

This is an observational, population-based multinational study of retrospective cohort design describing the occurrence of AESIs among subjects who received at least 1 dose of AZD1222 and among subjects who received AZD1222 as a first dose matched to subjects who had not yet received any COVID-19 vaccine.

9.2 Setting

This study, which is conducted in the VAC4EU (Vaccine Monitoring Collaboration for Europe, https://vac4eu.org/) research environment, uses a common protocol across all study sites, a common data model (CDM), and common analytics.

The analyses for interim report 1 were conducted using information collected in secondary automated electronic healthcare data sources in Europe. The data sources were Clinical Practice Research Datalink (CPRD) Aurum data in the UK, the Valencia Health System Integrated Database (VID) and SIDIAP database in Spain, the Regional Health Agency of Tuscany (ARS Toscana) database in Italy, and the PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research (PHARMO) in the Netherlands. These data sources were selected because they were able to capture the data elements needed to conduct this study, covered areas where AZD1222 use was expected, had been used in prior studies of vaccine safety, and appeared to have reasonably short data lags, which was necessary to conduct the interim analyses [38]. The study period varied by country and extended from the introduction of AZD1222 in each country in early 2021 through 13 October 2021 (see Table 4).

Table 4. Study Period in Each Study Data Source for Interim Report 1

Data source	CPRD Aurum (UK)	SIDIAP (Catalonia, Spain)	ARS Toscana (Italy)	PHARMO (Netherlands)
Date of the first dose of vaccine administration in the country	4 Jan 2021	9 Feb 2021	2 Feb 2021	12 Feb 2021
Lag time	1.5 months	6 months	3-4 months	3 months
Study period for interim report 1[a]	1 Jan 2021 to 13 Oct 2021 = 9.5 months after approval	1 Jan 2021 to 30 Jun 2021 = 5 months after approval	1 Feb 2021 to 31 Aug 2021 = 7 months after approval	1 Feb 2021 to 30 Jun 2021 = 5 months after approval

[a] Date ranges are inclusive.

Note that VID, the Valencia Health System Integrated Database, could not extract data for interim report 1.

ARS Toscana, Regional Health Agency of Tuscany; CPRD, Clinical Practice Research Datalink; PHARMO, PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research; SIDIAP, Information System for Research in Primary Care; UK, United Kingdom.

9.3 Subjects

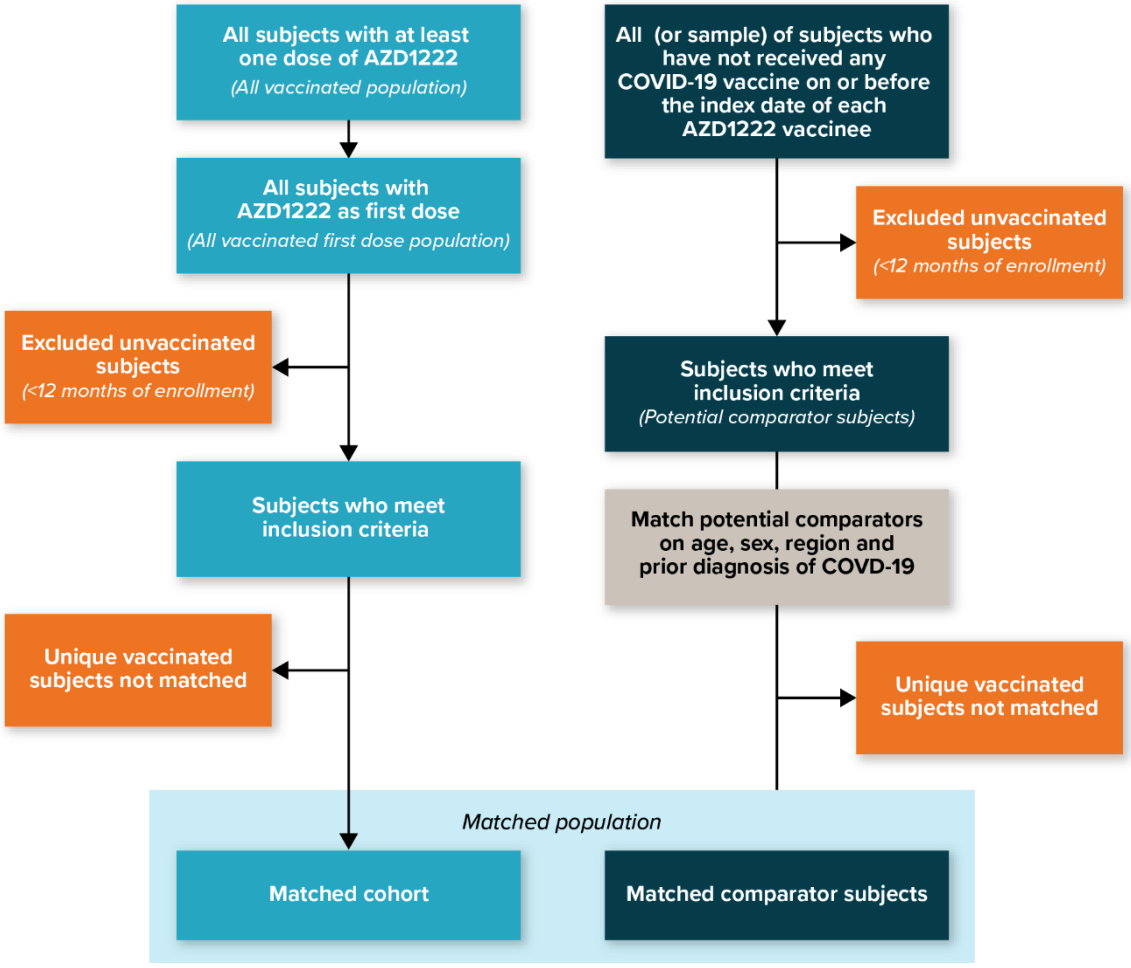
The source population for interim analysis 1 comprised all individuals registered in each data source during the study period. The study population included subjects who were exposed to the AZD1222 vaccine and concurrent subjects who did not receive any COVID-19 vaccine (who served as comparators).

Three different populations were identified among subjects exposed to AZD1222 (see Figure 1):

- *All vaccinated population*.
- *All vaccinated first dose population*.
- *Matched population*.

These populations are described in the following subsections.

Figure 1. Assembly of Study Cohorts



COVID-19, coronavirus disease 2019.

9.3.1 All Vaccinated Population

This population was included in the analysis to address the first objective of interim report 1 (ie, to describe the IRs of prespecified AESIs).

The *all vaccinated population* included all subjects vaccinated with at least 1 dose of AZD1222 during the study period. No other inclusion and exclusion criteria were applied. For each AESI, subjects who had an event of the specific AESI (see Table 5 in Section 9.4.2) during the clean look-back interval were excluded from the cohort included in the analysis for the specific AESI with which they had history, but not from the analysis cohorts for other AESIs.

The **index date** was the date when a subject received the first AZD1222 dose within the study period. Subjects who received AZD1222 after another COVID-19 vaccine as a second or third dose only were also included in this population.

9.3.1.1 Follow-up

For the assessment of each individual AESI, the subject's follow-up started at the index date and ended on the earliest of the following dates:

- The end date of the study period
- The subject's enrolment termination date in the health plan or system
- The subject's date of death
- The date on which the subject received a dose of any COVID-19 vaccine other than AZD1222
- For AESI-specific analyses, the date of the first diagnosis of a specific AESI recorded after the index date (for composite outcomes, follow-up was censored at the date of the first occurrence of any of the components).
- **For the evaluation of each AESI with known risk windows** (ie, those for which the end of the risk window in Table 5 in Section 9.4.2 was different from 180 or 365 days), the date on which the defined risk window for the last dose ends (the last dose was dose 1 if only 1 dose was received and dose 2 if 2 or more doses were received) (see Table 5 in Section 9.4.2)
- **For the evaluation of each AESI with unknown risk window** (those identified in Table 5 in Section 9.4.2 with a risk window that ended at 180 or 365 days), follow-up comprised all person-time after the index date and extended until 365 days after the last AZD1222 dose (dose 1 if only 1 dose was received and dose 2 if 2 or more doses were received).

9.3.2 All Vaccinated First Dose Population

This population was a subset of the *all vaccinated population* and included only those subjects that received AZD1222 as their first COVID-19 vaccine dose (subjects that received AZD1222 as their second or third COVID-19 vaccine dose were excluded). The **index date** was the date when a subject received the first AZD1222 dose as their first COVID-19 vaccine dose ever, ie, the subject had no other COVID-19 vaccine doses within the last 12 months, which included 1 year prior to AZD1222 and Moderna COVID-19 vaccine (Spikevax) commercialisation, but also around 10 to 11 months prior to Pfizer-BioNTech COVID-19 vaccine (Comirnaty) commercialisation. This population was included in the analysis to address the second objective for the interim report 1 (ie, to describe the timing and type of second dose of any COVID-19 vaccine (AZD1222 or other) over the study period among subjects having received a first dose of AZD1222).

9.3.3 Matched Population

This population comprised a vaccinated cohort matched with members of an unvaccinated cohort (*matched cohorts*), and it was used to address the first objective for the interim report 1 (ie, to describe the IRs of prespecified AESIs).

9.3.3.1 Inclusion Criteria

Subjects in the **vaccinated cohort** (see Figure 2) included those subjects in the *all vaccinated first dose population* that fulfilled all the following **inclusion criteria**:

- Received at least 1 dose of AZD1222 within the study period, and this was their first COVID-19 vaccine dose
- Had at least 12 months of data available before the index date
- Had no record of vaccination with any other COVID-19 vaccine on or before the index date

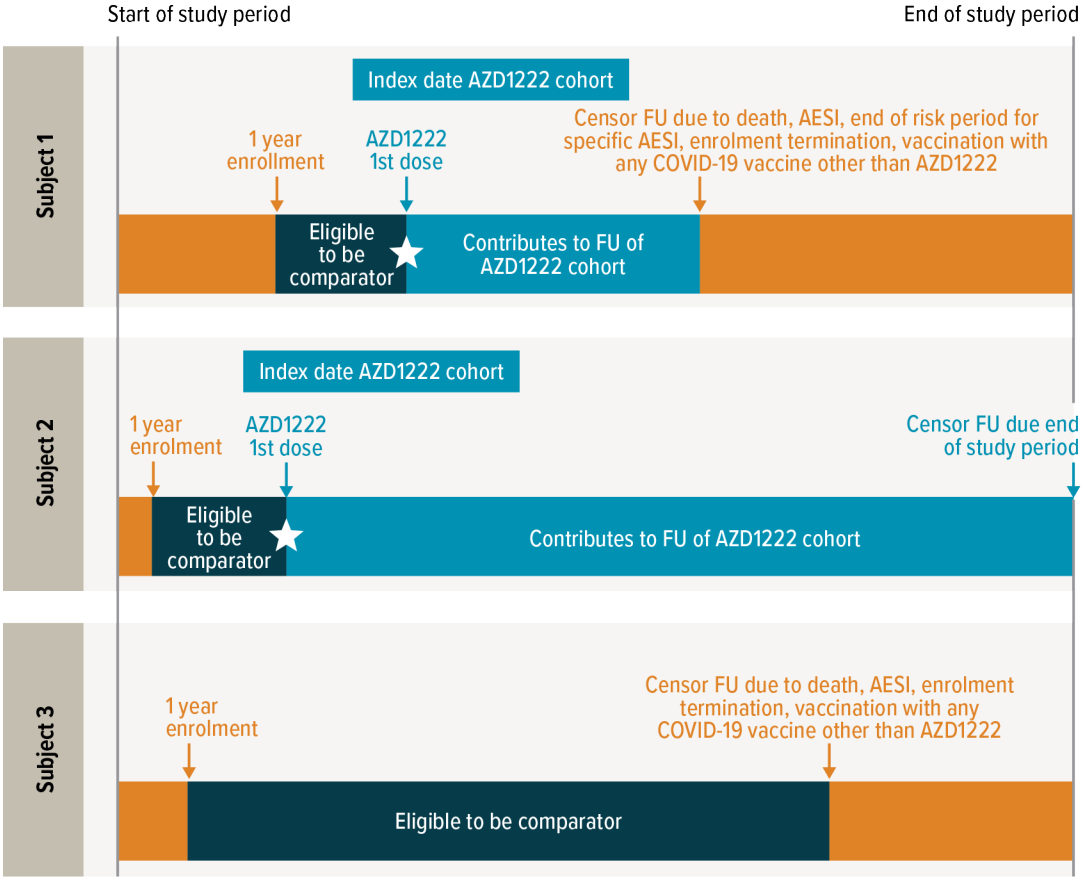
The **index date** was the date when a subject received the first AZD1222 dose within the study period.

A potential comparator subject (**unvaccinated cohort**) was eligible to be matched from the date the subject met all the following inclusion criteria:

- Had at least 12 months of prior data available.
- Had not received any COVID-19 vaccine, including AZD1222.

The **index date** for the unvaccinated subjects was assigned as the index date of the matched vaccinated subject.

Figure 2. Selection of the Vaccinated and Unvaccinated Cohorts and Identification of the Index Date: *Matched Population*



Note: In the figure, 1 year enrolment refers to the inclusion criterion to have at least 12 months of data available before the index date.
AESI, adverse event of special interest; COVID-19, coronavirus disease 2019; FU, follow-up.

9.3.3.2 Exclusion Criteria

The following exclusion criteria were considered in the **vaccinated** and **unvaccinated** cohorts:

- Subjects with missing values for any of the matching variables (age and sex) were excluded. No missing data were possible for the matching variable *prior COVID-19* since the absence of a code was considered to indicate absence of the disease.
- For each AESI, subjects (**vaccinated** or **unvaccinated**) who had a specific AESI (see Table 5 in Section 9.4.2) during the look-back period before the index date were excluded from the cohort for the analysis of that specific AESI, but not from the cohorts for analysis of other AESIs.
  - If a subject had the specific AESI between the index date and the start of the risk window or had any censoring criteria within this time period, the subject was excluded from the specific AESI analysis.

For the matched cohort design, if a vaccinated subject was excluded from analysis of a specific AESI due to having a prior history of that specific AESI, all its matched unvaccinated subjects were also excluded from that analysis. Analogously, if all unvaccinated subjects of a matched set were excluded, then the corresponding vaccinated subject was also excluded. If not all unvaccinated matched subjects of a matched set were excluded, the remaining unvaccinated subject(s) and the corresponding vaccinated subject were retained for the analysis. A description of the number of vaccinated subjects excluded because they had no matches and the number of unvaccinated subjects matched to each vaccinated subject is provided in the results in Section 10.1.

9.3.3.3 Matching Process

All unvaccinated subjects that were eligible at the index date of a vaccinated subject with the same age (± 2 years), sex, region, and prior diagnosis of COVID-19 were matched to this vaccinated subject, and the index date of the unvaccinated subject was assigned as the vaccination date of the matched vaccinated subject. Matching was done with replacement in a variable ratio of up to 1:5 vaccinated to unvaccinated. An unvaccinated subject could be matched to more than 1 vaccinated subject and therefore may have had different index dates.

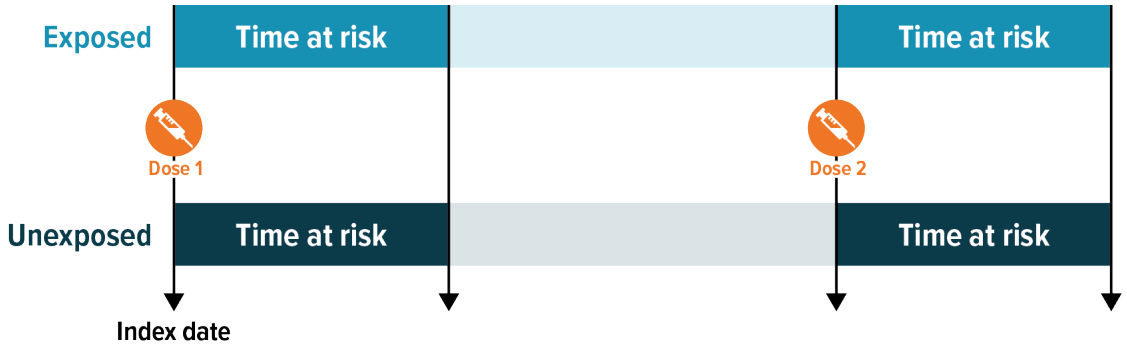
9.3.3.4 Follow-up

Follow-up for the vaccinated and unvaccinated started as detailed in the risk window for dose 1 for each AESI (see Table 5 in Section 9.4.2) and ended on the earliest of the following dates:

- The end date of the study period.
- The subject's enrolment termination date in the health plan or system.
- The subject's date of death.
- The date on which the subject received a dose of any COVID-19 vaccine other than AZD1222.
- For subjects in the unvaccinated cohort, the date on which the subject received a dose of AZD1222, at which time the subject switched from the unvaccinated cohort to the AZD1222 cohort.
- For AESI-specific analyses, the date of the first diagnosis of a specific AESI recorded after the index date (for composite outcomes, follow-up was censored at the date of the first occurrence of any of the components).
- For the evaluation of an **AESI with known risk window**, the end date of the defined risk window for the last dose (dose 1 if only 1 dose was received and dose 2 if 2 or more doses were received); this risk window applied to both vaccinated and matched unvaccinated subjects.

– For subjects who received 2 doses of AZD1222 and were not censored due to an AESI or other censoring criteria before the second dose, a second risk window followed the second dose; a corresponding second risk window was also applied for unvaccinated subjects mirroring the matched vaccinee (see Figure 3). Time between the end of the risk period after dose 1 and date of dose 2 was not considered as time at risk; however, if an AESI occurred during that period, the time at risk for dose 2 was not included.

Figure 3. Time at Risk for an AESI With Known Risk Window in Subjects With 2 Doses of AZD1222



AESI, adverse event of special interest.

- For the evaluation of an **AESI with an unknown risk window**, follow-up comprised all person-time after the index date and extended until 180 or 365 days (see Table 5 in Section 9.4.2) after the last AZD1222 dose (dose 1 if only 1 dose was received and dose 2 if 2 or more doses were received) for vaccinated subjects or the corresponding time for the unvaccinated.

The reasons for censoring were described to evaluate if there were differences between cohorts in the proportion of subjects censored due to informative (not administrative) reasons.

The extent to which unvaccinated subjects were vaccinated (and thus censored) is described in the current interim report 1.

9.4 Variables

9.4.1 Exposure

The exposure of interest was being vaccinated with AZD1222. Other vaccines for SARS-CoV-2 were identified for exclusion and censoring purposes. Identification of records for AZD1222 and other COVID-19 vaccines varied by data source.

Doses of AZD1222 were assessed by ordinal dose number of consecutive AZD1222 doses received, ie, subjects receiving AZD1222 as the first ever COVID-19 vaccine and a

subsequent AZD1222 dose were included in the analysis of second dose, and among these subjects, those who received another consecutive dose of AZD1222 were included in the descriptive analysis of a third dose. Some cleaning of the vaccination data was performed. If multiple records of a COVID-19 vaccine were found within 14 days after the first record, only 1 record was retained, with the first available brand and the first date as the date of the COVID-19 vaccine.

Receipt of AZD1222, other COVID-19 vaccines, and dates of vaccination were obtained from all possible sources that capture COVID-19 vaccination, such as pharmacy dispensing records, general practice records, and immunisation registers, as described below for each data source. Recording and availability of vaccination information for all data sources for interim report 1 was considered complete, except for PHARMO (see Section 9.4.1.5). See data source–specific details below.

9.4.1.1 CPRD, United Kingdom

In the CPRD, receipt of AZD1222, other COVID-19 vaccines, and dates of vaccination were obtained from general practice records via nationally used product codes, including batch numbers. All vaccinations in the UK are delivered by the public health system, recorded automatically in a clinical system at the point of care, and transferred automatically to the subject's medical record in the general practice system within 48 hours of entry into the point-of-care system. Recording and availability of vaccination information is expected to be complete in the vaccination registry used for this study.

9.4.1.2 VID, Valencia, Spain

In VID, data on receipt of AZD1222 and other COVID-19 vaccines, and dates of vaccination, were obtained from the Vaccine Information System (VIS), the vaccination registry included in the VID. Batch numbers will be available, as well as all information related to the vaccine and its administration. All vaccinations in Valencia are delivered by the regional public health system, automatically recorded in the system, and transferred to the vaccination registry. Recording and availability of vaccination information in the region of Valencia is expected to be complete in the vaccination registry used for this study.

9.4.1.3 SIDIAP, Catalonia, Spain

In SIDIAP, data on receipt of AZD1222 and other COVID-19 vaccines, and dates of vaccination, were obtained from the primary care electronic records; information includes brand name through the Anatomical Therapeutic Chemical (ATC) classification system. All vaccinations in Catalonia are delivered by the regional public health system, automatically recorded in the system, and transferred to the primary care records. Recording and availability of vaccination in the region of Catalonia were expected to be complete in the primary care records used in this study.

9.4.1.4 ARS Toscana, Tuscany, Italy

In ARS Toscana, data on receipt of AZD1222 and other COVID-19 vaccines, and date of vaccination, were obtained from the vaccine registry, which is included among administrative databases. All vaccinations in Tuscany are delivered by the regional public health system, automatically recorded in the system, and transferred in a standard electronic format to the regional database. Recording and availability of vaccination in the region of Tuscany was expected to be complete in the vaccination registry used in this study.

9.4.1.5 PHARMO, the Netherlands

Currently, in the Netherlands, different healthcare providers administer the COVID-19 vaccines (ie, general practitioners (GPs), the public health service, and healthcare institutions). The vaccination data are recorded in a central register (if people have given permission beforehand), the COVID-19 vaccination Information and Monitoring System. PHARMO is currently exploring the possibilities of linking with this register. Until then, and as described in the study SAP, the General Practitioner Database will be the basis for the vaccination data; thus, vaccine exposure may be underreported.

In the PHARMO Database Network, receipt of AZD1222 and other COVID-19 vaccines, and date of vaccination, were obtained from general practice records as found in the General Practitioner Database. The General Practitioner Database contains data on vaccinations administered by GPs and by the public health service (but not by healthcare institutions), as GPs receive an automated notification when a subject has a positive SARS-CoV-2 test or has been vaccinated via the public health service (provided that individuals have given their consent).

In PHARMO, due to the existence of multiple vaccination records per subject in the GP data, a process of data cleaning prior to the transformation step of the extraction, transformation, and loading (ETL) process was needed. However, the conservative process that was systematically used assigned all doses of COVID-19 vaccines to “unknown” vaccine when heterologous schemes were identified, ie, when first and second doses were not from the same manufacturer. For this reason, the number of subjects vaccinated with AZD1222 is likely underestimated. The data-cleaning process in PHARMO has been identified as an area of correction for the next interim analysis.

9.4.2 Outcomes

See Table 5 for a list of the AESIs included in the AZD1222 PASS. The table includes the clean look-back interval (the period before cohort entry for each AESI during which the specific AESI for the analysis must not be observed) and the risk window after the index date. Only the first occurrence of each AESI during the follow-up period qualified as an outcome.

Outcomes were identified using algorithms based on codes for diagnoses in electronic data, and they were defined uniformly across the data sources to the fullest extent possible. Operational case definitions for the AESIs were developed in collaboration within the VAC4EU environment (https://zenodo.org/communities/vac4eu), using the ACCESS project as a starting point. Risk windows were based on consensus definition from the AESI Working Group of Vaccines Europe, March 2021, or on Lee et al [22] or on COVID-19 Vaccine Safety Surveillance: Active Monitoring Master Protocol [13]. When no consensus evidence for a risk period was identified, ie, "unknown risk window," the risk window was defaulted to 180 or 365 days after the index date. Risk windows that were short and based on existing literature or consensus were defined as "known" (those for which the end of the risk window is other than 180 or 365 days, except for anaphylaxis and sudden death) and risk windows that were long or for which there was no consensus evidence were defined as "unknown" (those with a risk window assigned to end at 180 or 365 days).

For the definition of AESIs, only codes tagged as "narrow" were used, except for acute aseptic arthritis, for which no specific codes were available and instead "possible" codes such as gout, arthritis, chondrocalcinosis, and crystal arthropathies were used to identify events. For some coding systems such as ICD-9-CM and International Classification of Primary Care (ICPC), there are few or no codes to define some of the outcomes, for example, fibromyalgia or multisystem inflammatory syndrome. In PHARMO, some outcomes were also ascertained through free-text searches in addition to ICPC codes, which are very high-level and agranular codes. For some other coding systems such as SNOMED, which is used in CPRD, the granularity of the coding allowed evaluation of postural orthostatic tachycardia and capillary leak syndrome, which are not defined in any other coding system. Therefore, some AESIs could not be assessed in some data sources; these have been indicated as NA (not available) in the tables of results.

Table 5. Adverse Events of Special Interest

Adverse event of special interest	Clean look-back interval (days)[a]	Risk window (days after index date)
Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease, including ARDS	365	14-365[b]
Multisystem inflammatory syndrome in adults/children	365[c]	1-42[c]
Sudden death	Not applicable	0-6[b]
Autoimmune thyroiditis	365	1-180[e]
Anosmia, ageusia	365	1-365[e]
Anaphylaxis	180[c]	0-2[c]
Type III hypersensitivity reactions	365	1-365[e]
ARDS	365	1-28[g]
Guillain-Barré syndrome	365[c]	1-42[c]

Adverse event of special interest	Clean look-back interval (days)[a]	Risk window (days after index date)
Other peripheral and polyneuropathies	365[c]	1-42[c]
Multiple sclerosis[e], and other demyelinating disorders[e]	365[c]	1-365[e]
Transverse myelitis	365[c]	1-90[c]
Optic neuritis/neuromyelitis optica spectrum disorder	365[c]	1-42[c]
Encephalitis (including acute disseminated encephalomyelitis)	183[c]	1-42[b]
Myasthenia gravis	365	1-365[e]
Bell's palsy	365[c]	1-42[c]
Generalised convulsions	365	0-14[c]
Narcolepsy	365[c]	1-42[c]
Myocarditis/pericarditis	365[c]	1-42[c]
Postural orthostatic tachycardia syndrome	365[c]	1-42[b]
Myocardial infarction	365[c]	1-28[c]
Acute cardiac injury including microangiopathy, cardiogenic shock, heart failure, stress cardiomyopathy	365	1-90[e]
Stress cardiomyopathy	365	1-42
Thrombocytopaenia	365[c]	1-42[b]
Thrombocytopaenia with associated bleeding	365[c]	1-42[h] (Sensitivity analysis: 1-28)[i]
Thrombosis (embolic and thrombotic events) without thrombocytopaenia	365[c]	1-42[c]
Thrombosis with thrombocytopaenia syndrome	365	1-42[h] (Sensitivity analysis: 1-14, 1-21, and 1-28)[i]
Capillary leak syndrome	365	1-365[e]
Acute kidney injury	365	1-14[b]
Acute liver injury	365	1-14[b]
Acute pancreatitis	365	1-365[e]
Acute aseptic arthritis	365	1-42[b]
Fibromyalgia	365	91-365[j]
Rhabdomyolysis	365	1-42[b]
Chronic fatigue syndrome/ME/PVFS	365	183-365[k]
Erythema multiforme	365	1-365[e]
Chilblain-like skin lesions	365	1-365[e]

[a] Clean interval refers to the look-back period before the index date during which the specific AESI being analysed must not have been observed. Unless indicated otherwise, the duration is based on the clinical judgement of the research team.

[b] Risk window based on consensus definition from the AESI Working Group of Vaccines Europe, March 2021.

[c] Based on Lee et al [22] or COVID-19 Vaccine Safety Surveillance: Active Monitoring Master Protocol [13].

[d] Not addressed in the ACCESS protocol template but is deemed not suitable for 1 or more of the following reasons: onset may be gradual, the diagnosis date may substantially lag the onset of symptoms, or the risk period is not clearly established.

[e] No consensus evidence for a risk period was identified; defaults to 1 year after the index date.

[f] Footnote from original protocol table was applicable only to the self-controlled risk interval.

[g] Based on Serazin et al [32].

[h] Sensitivity analyses evaluated alternative risk windows. For TTS, they were 1 to 14, 1 to 21, and 1 to 28 days after the index date. For thrombocytopaenia with bleeding, the alternative risk window was 1 to 28 days after the index date, following Pottegård et al [28].

[i] Sensitivity analysis were not performed in interim analysis 1.

[j] No consensus evidence for a risk period was identified. However, because symptoms need to be present for at least 3 months before subjects qualify for the diagnosis [2], the start of the risk window was set to 91 days after the index date.

[k] No consensus evidence for a risk period was identified. However, because chronic fatigue needs to be present for at least 6 months before subjects qualify for the diagnosis [20], the start of the risk window was set to 183 days after the index date.

Note: Risk window definitions may evolve during the course of the study as more knowledge is gathered about individual AESIs.

AESI, adverse event of special interest; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; FDA, Food and Drug Administration; IOM, Institute of Medicine; ME, myalgic encephalitis; PVFS, postviral fatigue syndrome; TTS, thrombosis with thrombocytopaenia syndrome.

Given the clinical relevance of TTS, the event definition for TTS for this study is included here. The clinical definition requires

- A new qualifying thromboembolic event (defined below) AND
- A new diagnosis of thrombocytopaenia (or laboratory evidence of the same, where available) that was made from 10 days before and up to 10 days after the thromboembolic event date.

Thromboembolic events included new diagnoses of embolism or deep vein thrombosis (DVT) (including splanchnic, intracranial, limb locations) or thromboembolism. According to the working event definition, infarctions (including myocardial and cerebral) and stroke did not qualify as thromboembolic events. In addition to evaluating thromboembolic events overall, in future interim analyses, the research team proposed to evaluate thromboembolism outcomes separately by location of the thrombus: central venous sinus thrombosis, limb thrombosis, and splanchnic area thrombosis.

This definition was initially built on the initial proposal discussed within VAC4EU (https://youtu.be/-Sp5GKfzB2I), and the definition forms for coagulation disorders are available online (https://zenodo.org/record/5255870#.Ykwue99ByUk).

In the primary analysis, the risk window for TTS extended from 1 to 42 days after the index date. Sensitivity analyses are planned to evaluate alternative risk windows of 1 to 14 days, 1 to 21 days, and 1 to 28 days after the index date. This sensitivity analysis will be prepared in future interim analyses. A validation of the TTS outcome will be performed at the time of final analysis.

9.4.3 Covariates

As per the AZD1222 SAP, calendar time, age, sex, region, and prior COVID-19 at the index date were used in the analyses for interim report 1 as matching variables.

Geographic region was defined as the region, department, healthcare district, postal code, or GP practice where the subject was located at the index date.

Prior COVID-19 was defined as having a COVID-19 diagnosis or a positive PCR (polymerase chain reaction) or antigen test any time before the index date. Absence of a diagnosis or positive test was considered to indicate absence of the disease.

9.5 Data Sources and Measurement

9.5.1 CPRD, United Kingdom

The CPRD collates the computerised medical records of a network of GPs in the UK who have acted as the gatekeepers of healthcare and maintained subjects' life-long electronic health records since 1987. The data are sourced from over 2,000 primary care practices and include 62 million subjects, of whom 16.5 million are currently registered and active [25]. General practitioners act as the first point of contact for any non-emergency health-related issue, which may then be managed within primary care and/or referred to secondary care, as necessary. Secondary care teams also provide feedback information to GPs about their subjects, including key diagnoses. The data in the CPRD are updated monthly and include demographic information, prescription details, clinical events, preventive care, specialist referrals, hospital admissions, and major outcomes, including death [17; 40]. Most of the data are coded using Read or SNOMED codes. Data validation with original records (specialist letters) is available.

Depending on the type of electronic medical software used by the general practice, data are collected into either the CPRD GOLD (General Practitioner Online Database) or the CPRD Aurum database. Data include demographics, all GP/healthcare professional consultations, diagnoses and symptoms, results from laboratory tests, information about treatments (including prescriptions), data on referrals to other care providers, hospital discharge

summaries (date and Read/SNOMED codes), hospital clinic summaries, preventive treatment and immunisations, and death (date and cause). Lag time for CPRD Aurum is usually 1 month, although this may be extended due to CPRD database technical updates. Information about vaccinations from mass vaccination campaigns during the pandemic is expected to transfer to GPs and into the subject's medical records (via National Health Service [NHS] systems rather than subjects informing the GP); however, the lag time for this transfer is not yet clear.

Linkage of the CPRD primary care data with other subject-level datasets is available for English practices that have consented to participate in the linkage scheme. In more than 80% of the CPRD panel practices, the GPs have agreed to permit the CPRD to link at the subject level to these subject-level datasets. The Hospital Episode Statistics (HES) database contains details of all admissions to NHS hospitals in England (Accident and Emergency, Admitted Subject Care, and Outpatient); approximately 46.8 million individuals in the CPRD are linked to the HES database. Not all subjects in the CPRD have linked data (eg, if they live outside England, if their GP has not agreed that their data may be used in this way). As with standard CPRD subjects, HES data are limited to subjects with research-standard data. The CPRD records are linked to the HES using a combination of the subject's NHS number, sex, and date of birth [39]. Additional CPRD-linked datasets include Death Registration data from the Office for National Statistics, which includes information on the official date and causes of death (using International Classification of Diseases codes), and the Mother-Baby Link and an algorithm-based Pregnancy Register, which are available only with CPRD GOLD.

In addition, other CPRD-linked COVID-19 datasets, which may provide further follow-up information on AESIs, include the Public Health England (PHE) Second Generation Surveillance System (SGSS) COVID-19–positive virology test data, PHE COVID-19 Hospitalisation in England Surveillance System (CHESS), and the Intensive Care National Audit and Research Centre (ICNARC) data on COVID-19–related intensive care admissions.

Linked datasets are usually updated every 6 months, and the lag time between data recording and data availability varies by dataset. The latest linkage set (set 21) contains an update of priority linkages to support COVID-19 research, along with the CPRD-linked SGSS COVID-19–positive virology test data and CHESS hospitalisation and intensive care unit/high dependency unit data up to the end of September 2020.

The present study included active CPRD Aurum practices. These practices include an estimated 13.4 million current subjects. CPRD is listed under the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) resources database, and access was provided by the Drug Safety Research Unit (DSRU).

For interim analysis 1, CPRD Aurum without additional linkages was used.

9.5.2 VID, Valencia, Spain

Data from VID could not be extracted to be included in interim report 1.

Access to the regional databases for the Valencia region is managed by the Valencia Public Health System (Conselleria de Sanitat). The research team at FISABIO (Foundation for the Promotion of Health and Biomedical Research of Valencia Region) obtained the ethics approval on 18 October 2021. Permission to access the databases of the Valencia Public Health System was obtained on 17 November 2021. The codes for data to be extracted from the different VID databanks were requested on 3 December 2021. Data extraction depends on the Valencia Public Health System. Each of the different data banks (eg, primary care vs hospital) is managed by a different department within the Valencia Public Health System. As of 21 April 2022, FISABIO had not received all the data banks needed to perform the analysis; no information regarding dates of extraction for the data banks that are pending was available. Data from VID will be analysed as soon as all data banks become available, and results will be shared with the EMA in the next interim report.

The VID is a set of population-wide electronic databases covering residents of the Valencia region in Spain, representing approximately 5 million individuals [14]. All the information in the VID can be linked at the individual level through a single personal identifier. The datasets in the VID are as follows:

- The Population Information System (SIP) is a database that provides basic information on health system coverage (eg, dates and causes of Valencia health system entitlement or disentitlement, insurance modality, pharmaceutical copayment status, and assigned healthcare department), as well as some sociodemographic data (eg, sex, date of birth, nationality, employment status, and geographic location) since 2011. Importantly, the SIP database includes the date of death captured from the Mortality Registry. The SIP database is paramount to the VID, as it is the source of the individual, exclusive, and permanent identifier number associated with each individual (the SIP number), which is then used throughout the rest of the databases, thereby allowing data linkage across the multiple databases in the network.
- The Ambulatory Medical Record (ABUCASIS) is the electronic medical record for primary and specialised outpatient activity, with 96% population coverage since 2009. ABUCASIS is integrated by 2 main modules: the Ambulatory Information System (SIA) and the Pharmaceutical Module (GAIA), including paediatric and adult primary care, mental healthcare, prenatal care, and specialist outpatient services, as well as providing information about dates, visits, procedures, laboratory test results, diagnoses, and clinical and lifestyle information. ABUCASIS also includes information on several health programmes (eg, healthy children, vaccines, pregnancy, notifiable diseases), the primary care nurse clinical record, and the health-related social assistance record.

  - The SIA module uses the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) for coding diagnoses (and, partially, the International Classification of Diseases, 10th Revision, Spanish Edition [ICD-10-ES] from 2019). The SIA also uses the Clinical Risk Groups system to stratify the morbidity of the entire population.
  - GAIA stores data on all outpatient pharmaceutical prescriptions and dispensing, including both primary care and outpatient hospital departments, using the ATC classification system and the National Pharmaceutical Catalogue, which allow the identification of the exact content of each dispensing. GAIA does not include in-hospital medication or medication administered in the accident and emergency department (AED). GAIA provides detailed information on prescriptions issued by physicians, such as the duration of treatment and dosage. GAIA started in 2006, but data are considered more reliable since 2008.

- The Hospital Medical Record database (ORION) provides comprehensive information covering all areas of specialised care: admission, outpatient consultations, hospitalisation, emergencies, diagnostic services (eg, laboratory tests, imaging, microbiology, pathology), pharmacy, surgical block including day surgery, critical care, prevention and safety, social work, at-home hospitalisation, and day hospitalisation. ORION is currently in the process of being integrated for the whole region, with several databases already fully integrated and available for all hospitals, including the Minimum Basic Data Set at Hospital Discharge (MBDS) and the AED clinical record.
  - The MBDS is a synopsis of clinical and administrative information on all hospital admissions and major ambulatory surgery in the Valencia health system hospitals, including public-private partnership hospitals (approximately 450,000 admissions per year in the region) since 2006. The MBDS includes admission and discharge dates, age, sex, geographic area and zone of residence, main diagnosis at discharge, up to 30 secondary diagnoses (comorbidities or complications), clinical procedures performed during the hospital episode, and the diagnosis-related group(s) assigned at discharge. The MBDS used the ICD-9-CM system for coding through December 2015 and ICD-10-ES afterward. The MBDS was extended in 2015 to include the "present on admission" diagnosis marker and information on tumour morphology.
  - The AED clinical record was launched in 2008 and collects triage data, diagnoses, tests, and procedures performed in public emergency departments. As with the MBDS, the system used ICD-9-CM coding until December 2015 and ICD-10-ES thereafter. Diagnosis codification has been increasing from approximately 45% of all emergency department visits between 2008 and 2014 to approximately 75% in 2017, largely due to the progressive incorporation of hospital coding.
- Data on vaccine exposure may be obtained from the VIS, which includes information on vaccine type, manufacturer; batch number; number of doses; location and administration

date; adverse reactions related to vaccines; and, if applicable, risk groups. Information in the VIS is updated daily.

All databases included in the VID are updated frequently (every 1 to 3 months), except the MBDS database, which is updated every 6 months. Access to VID data is provided by FISABIO.

For interim report 1, linked data from the MBDS were not available.

9.5.3 SIDIAP, Catalonia, Spain

The Information System for Research in Primary Care (SIDIAP) in Catalonia, Spain, is a primary care database launched in 2010 by the Institute of Research in Primary Care (IDIAP Jordi Gol) and Catalan Institute of Health (Institut Català de la Salut). The database collects information from 278 primary healthcare centres and includes more than 5.8 million subjects covered by the Catalan Institute of Health (approximately 78% of the Catalan population) and is highly representative of the Catalan population [38].

SIDIAP data comprise the clinical and referral events registered by primary care health professionals (ie, GPs, paediatricians, and nurses) and administrative staff in electronic health records, comprehensive demographic information, community pharmacy invoicing data, specialist referrals, and primary care laboratory test results. For this project, SIDIAP has been linked to the hospital discharge database, which has been available since 2010 and is updated twice a year. Health professionals gather this information using ICD-10 codes, ATC codes, and structured forms designed for the collection of variables relevant to primary care clinical management, such as country of origin, sex, age, height, weight, body mass index, tobacco and alcohol use, blood pressure measurements, and blood and urine test results. In relation to vaccines, information on all routine childhood and adult immunisations is included, in addition to the antigen and the number of administered doses.

Currently, because of the COVID-19 pandemic, having shorter-term updates to monitor the evolution of the pandemic is a possibility. Recent reports have shown SIDIAP data to be useful for epidemiological research. SIDIAP is listed under the ENCePP resources database (www.encepp.eu/encepp/resourcesDatabase.jsp) and was characterised in the IMI-ADVANCE project and considered fit for purpose for vaccine coverage, benefits, and risk assessment (http://www.encepp.eu/encepp/viewResource.htm?id=4646).

9.5.4 ARS Toscana, Tuscany, Italy

ARS Toscana is a research institute of the Tuscan regional government. Tuscany is an Italian region with approximately 3.6 million inhabitants. The ARS Toscana database comprises all the data that are collected in Tuscany related to healthcare delivered to those who are official residents of the region. Additionally, ARS Toscana collects data tables from regional initiatives.

The ARS Toscana database routinely collects primary care (since 2003) and secondary care (since 2004) prescriptions for drugs for outpatient setting use and is able to link them at the individual level with hospital admissions available since 1997, admissions to emergency care available since 2009 (but complete since 2012), records of exemptions from copayment, dispensing of diagnostic tests and procedures, causes of death, and a pathology registry, which has been available for the last few years and includes complete information only for morphology and topography. Occasionally, ARS Toscana may request retrieval of information from medical records or laboratory results regarding specific subpopulations and link this information to its core data.

Subjects in ARS Toscana can be characterised in terms of age, sex, comorbidities (via algorithms), socioeconomic indicators, medication taken regularly on an outpatient basis, date of death, and healthcare utilisation (including visits to specialists, visits to ambulatory cancer care units, and visits to an emergency department or urgent care centre). Cause of death is available with a lag time of 3 years.

The lag time from a healthcare encounter to incorporation of data for research purposes is approximately 3 to 4 months. All subjects in the ARS Toscana database can be linked to mortality data through deterministic linkage. There is no restriction on reporting small numbers.

Participation of the ARS Toscana database in a research study includes mandatory compliance with the ENCePP Code of Conduct [11], which "provides a set of rules and principles for pharmacoepidemiology and pharmacovigilance studies to promote scientific independence and transparency throughout the research process."

9.5.5 PHARMO, the Netherlands

The PHARMO Database Network, which is maintained by the PHARMO Institute for Drug Outcomes Research, is a population-based network of electronic health record databases that combines anonymous data from different primary and secondary healthcare settings in the Netherlands. These different data banks—including data from general practices, inpatient and outpatient pharmacies, clinical laboratories, hospitals, the cancer register, the pathology register, and the perinatal register—are linked at the subject level through validated algorithms. To ensure data privacy in the PHARMO Database Network, the collection, processing, linkage, and anonymisation of the data are performed by STIZON, which is an independent, ISO/IEC 27001–certified foundation that acts as a trusted third party between the data sources and the PHARMO Institute. The PHARMO Institute is always seeking new opportunities to link with additional databanks and is currently exploring linkage with the COVID-19 immunisation register, which is collected by the Dutch National Institute for Public Health and the Environment.

Currently, the PHARMO Database Network covers over 6 million persons of 17 million inhabitants of the Netherlands. Data collection period, catchment area, and overlap between data sources differ. Therefore, the final cohort size for any study depends on the data sources included. All electronic subject records in the PHARMO Database Network include information on age, sex, socioeconomic status, and mortality. Other available information depends on the data source. The lag time of all databases is 1 year, except for the General Practitioner Database, which is updated every 3 months or less. A detailed description of the different data sources is given below [38].

- The Hospital Database: Hospital admissions include discharge dates, discharge diagnoses, and procedures for hospitalisations longer than 24 hours (or shorter if the subject required a bed). Hospital discharge diagnoses are available from the Dutch National Basic Hospital Care Registration (Landelijke Basisregistratie Ziekenhuiszorg [LBZ]) and are recorded using ICD-10 codes since 2013. Procedures are coded according to the Dutch Hospital Data Foundation registration system.
- The General Practitioner Database comprises data from electronic medical records registered by GPs from 2003 onwards. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists, and healthcare product/drug prescriptions. Primary care data are available for a portion of the population of approximately 3.2 million inhabitants (approximately 20% of the Dutch population). Information on lifestyle variables (eg, body mass index, smoking, alcohol consumption) is available in the General Practitioner Database if recorded by GPs in the electronic medical records.
- The Out-subject Pharmacy Database comprises GP-prescribed or specialist-prescribed healthcare products dispensed by the outpatient pharmacy since 1990. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty, and costs. Drug dispensations are coded according to the ATC classification system. Outpatient pharmacy data cover a catchment area representing 4.2 million residents (~25% of the Dutch population).

Analysis for interim report 1 was based on the General Practitioner Database only.

9.6 Bias

Potential biases were addressed as follows:

- Exposure misclassification: Exposure identification was based on pharmacy dispensing records, general practice records, immunisation registers, medical records, or other secondary data sources. The ability to identify specific COVID-19 vaccine products and dates of vaccination in the participating data sources is considered complete, except in PHARMO (see Section 9.4.1). The self-controlled risk interval (SCRI) design, which

includes only individuals who are known to be vaccinated, will also address remaining concerns in this area.

- Outcome misclassification: Outcome identification relied on the accuracy of codes and algorithms to identify outcomes and the data available in each data source.
  - To reduce the probability of outcome misclassification, this study used the codes and algorithms proposed by ACCESS, when available. These codes and algorithms are based on literature reviews, have been reviewed by epidemiologists and medical experts, and have been used in the "Background rates of AESI protocol" (EUPAS37273). For those AESIs not available in ACCESS, AESIs were defined uniformly across the data sources to the fullest extent possible. For TTS, identification algorithms will be validated using manual review of electronic records or chart abstraction in the final analysis of the AZD1222 PASS.
  - For interim report 1, the data extraction was performed during Q1 2022. Due to the lag time in the data sources (see Section 9.2, Table 4), for some of the AESIs the risk window as defined in Table 5 was not fully covered. Therefore, the possibility that IRs were underestimated cannot be fully rejected. In future analyses (ie, for interim reports 2 and 3 and the final analysis), at least 1 year of follow-up will be included, thereby minimising this risk of outcome misclassification.
- Detection bias can occur when knowledge of exposure leads to differential intensity of outcome ascertainment. A vaccinated individual may be more attuned to the possibility of an adverse reaction after vaccination and have a different threshold for seeking medical evaluation of symptoms than someone who is unvaccinated. Concerns that publicity about potential adverse effects may lead to differential ascertainment over time will be addressed through inspection of IRs in sequential periods at the time of the final analysis.
- Uncertainty about risk periods may lead to misclassification and potential attenuation of risk estimates in the cohort design. For AESIs with gradual onset, such as multiple sclerosis or peripheral neuropathies, the date of disease onset will likely precede the date of first recorded diagnosis; for events diagnosed shortly after vaccination, there is the possibility that the order of events (exposure/outcome) may actually be reversed. These concerns can be partially addressed through sensitivity analyses that introduce lag intervals. Approaches to address this limitation will be addressed at the time of final analysis.
- This study plans to estimate the risk of AESIs among subjects who have been vaccinated compared with unvaccinated subjects with similar health conditions. Subjects who did not receive vaccination (or received it later) may have different health status and patterns of healthcare compared with those who are vaccinated. These differences may include a higher prevalence of frailty or underlying chronic conditions [37] among vaccinees. In studies involving vaccines, special attention should be given to bias related to healthy vaccinee bias and confounding by indication [29]. Healthy vaccinee bias refers to the

situation in which subjects who have better health conditions are more likely to be vaccinated; thus, confounding by indication may be present if subjects with underlying chronic diseases are more likely to be vaccinated than healthy study subjects. Although both situations could occur in this study, at the beginning of the study period, vaccination was preferentially directed to subjects with more underlying conditions. To address these potential bias/confounding issues, the current study was designed to first match subjects in the vaccinated cohort with comparators of the same age, sex, and at the same calendar date. In future interim and in the final analysis, subjects will also be matched by special population status (which includes frailty indicators or immunocompromised conditions) and propensity scores will also be used to adjust for potential confounders, including patterns of prior healthcare use.

- Confounding: It was expected that the subject groups targeted for vaccination would change over the course of the study in all countries. Matching on calendar date, age, and prior COVID-19 partially addressed this concern and also reduced potential confounding due to changing patterns of SARS-CoV-2 infection and for changes in healthcare–seeking behaviours that had been observed during the pandemic. However, remaining unvaccinated may also be related to lifestyle choices that are difficult to measure in electronic healthcare data sources. Failure to account for variables that are unmeasured (or imperfectly measured) may lead to residual confounding [37]. The potential effect of an unmeasured confounder will be evaluated using bias analysis in future reports. To address potential confounding, the SCRI design will be used in the final analysis, which automatically adjusts for time-invariant confounders, and using only postvaccination control periods will avoid the potential bias that use of prevaccination control periods may introduce, as prevaccination health events may affect the probability of exposure. However, the SCRI design is not well suited to study outcomes with gradual onset, long latency, or risk periods that are not well known.
- Selection bias: It is conceivable that over the study period, as more of the population has received vaccines to prevent COVID-19, the population of potential comparators will dwindle or that people who remain unvaccinated may be systematically different from those choosing to be vaccinated. Additionally, the age restrictions in the use of AZD1222 imposed in the UK, Spain, Italy, or the Netherlands may make it difficult to find comparable controls for the cohort study. If such a scenario develops,
  - The SCRI analysis, which includes only vaccinated individuals, as the primary analysis to evaluate vaccine/AESI associations for outcomes that are suitable for this design. The SCRI analysis will be conducted at the time of final analysis.
  - Using historical control subjects could also be considered. However, due to concerns over non-comparability, the use of historical controls is not the best alternative at this stage. The background rate of AESIs may have changed during the pandemic due to the effects of COVID-19 and/or because of access issues or changes in health-seeking

behaviours. Therefore, should concurrent unvaccinated comparators not be feasible, the preference at this stage is for active (vaccinated) comparators to be used; however, this approach is not without challenges due to the specific and time-varying vaccination policies in each country and even within regions. In this interim report 1, the availability of concurrent unvaccinated comparators and the duration of their follow-up time were monitored and are presented in Section 10.2.2.

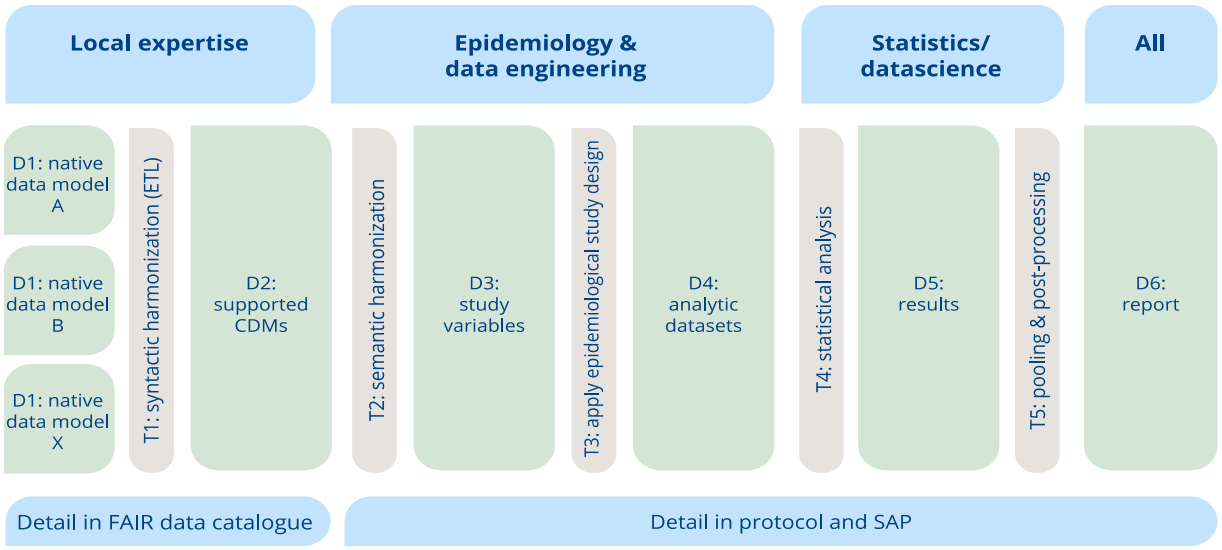
9.7 Study Size

For interim report 1, no comparative analyses were performed. All subjects exposed to the AZD1222 were included.

9.8 Data Transformation

The following transformation steps (T) were implemented (see Figure 4):

Figure 4. Data Transformation Process



CDMs, common data models; D*n*, data type; ETL, extract, transform, and load; FAIR, findable, accessible, interoperable, and reusable; T*n*, transformational step (for explanation, see below).

9.8.1 T1: Syntactic Harmonisation (ETL)

T1: Syntactic harmonisation through an ETL process of native data into the ConcePTION CDM [6]. In this CDM, data are represented using a common structure, but the content of the data remain in their original format. The CDM version that was used was v2.2, which is available as an open-source CDM. The CDM was developed as part of the IMI-ConcePTION project (project number IMI-821520). The ETL process had various structured steps as described in Thurin et al [34]:

1 Data access partners (DAPs) were asked to share the data dictionaries of their data banks (tables and variable names/structure) with the principal investigator of the study.
2 Based on the data dictionaries of the data banks, an interview was conducted by the Principal Investigator that explored what action(s) prompted the creation of a record, what was missing, and the context of each of the data banks.
3 Metadata (descriptive data about the data sources and databanks), data dictionaries, and interview answer sheets will be uploaded in the VAC4EU FAIR (findable, accessible, interoperable, and reusable) data catalogue, according to the metadata structure for electronic health data that was defined in IMI-ConcePTION and the EMA-funded MINERVA project.
4 An overview was created of all the required study variables and definitions in order to create the code lists to identify the outcomes and covariates (see T2).
5 Instructions for the ETL design were provided by the scientific coordinator, these instructions comprised the required CDM tables, mandatory variables, the calendar period over which data need to be extracted, and the code lists for the data to be extracted.

Once the ETL design was approved, it was executed by each DAP using its programming language. The output files were CSV (comma-separated values) files. Once the ETL was conducted, Level 1 and 2 data quality checks were conducted to measure the integrity of the ETL, as well as internal consistency within the context of the CDM.

1 Level 1 data checks were performed to assess the completeness and content for each variable in all CDM tables to ensure that the mandatory variables contain data and conform to the formats specified by the CDM specifications.
2 Level 2 data checks were performed to assess the logical relationship and integrity of data values within a variable, or between 2 or more variables within and between tables.

9.8.2 T2: Semantic Harmonisation

To reconcile differences between terminologies and native data availability, a shared semantic foundation was applied for the creation of study variables. This was a multistep process:

1 Definition of study variables, which was done using an event definition form and was a living document that will be closed upon AZD1222 PASS ending.
2 Initial code lists were created using the VAC4EU CodeMapper tool (https://vac4eu.org/codemapper/) which was developed during the IMI-ADVANCE project to assist in the creation of code sets from event definitions for several coding systems simultaneously while keeping a record of the complete mapping process.
3 Study variables are named in a standard hierarchical fashion based on body system.
4 Review of the codes by DAPs.

5 Consolidation: Comments from DAPs were consolidated by the study team.

6 Based on the relevant diagnostic medical codes and keywords, the algorithms were constructed to operationalise the measurement of each study variable. These algorithms could differ by database, as the components relevant for the study variables may differ.

7 During the T2 step, transformations occurred for a series of steps related to completion of missing features in the data, eg, dose of vaccines, sorting on record level, combination of concepts for algorithm, and rule-based creation of study variables on a personal level for the study population (specific, if needed, per DAP).

8 Once the study variables were created, Level 3 checks were deployed, which were targeted to assess the patterns of study variables.

9.8.3 T3: Application of the Epidemiological Study Design

Based on the creation of the study variables on a person level or a medicines level, epidemiological designs were applied. Specifically, matching on specific variables and selection based on inclusion and exclusion criteria.

For CPRD and PHARMO, before extensive medical data could be extracted, preliminary matching of vaccinated persons and comparators on key demographic characteristics (eg, age, sex, region, and prior COVID-19) was needed since not all of the medical data could be extracted for the D1 data instance.

9.8.4 T4: Statistical Analysis

This step in the data transformation pipeline produced statistical estimates such as descriptives (counts, percentages), distributions (mean, percentiles), and rates (prevalence, incidence). This was conducted using R.

Scripting and Deployment

The analytical R scripts that produced the T2-T4 steps were produced on VAC4EU GitHub for version control; links to the latest script were distributed to DAPs for local deployment. Any issues were notified, and the data engineers who were responsible for the R code worked with the local DAP to resolve issues. Scripts were developed independently, based on data engineering programmes and the codebook in R (by University Medical Center Utrecht [UMCU]) was validated using SAS (by RTI Health Solutions [RTI-HS]), comparing the output from both analysis programs was against each other for consistency.

9.8.5 T5: Results and Pooling After Processing

The aggregated results produced through T4 were uploaded to the Digital Research Environment (DRE) for pooled analyses and visualisation (T5, Figure 4). The DRE was made available through VAC4EU and UMCU [33]. The DRE was a Microsoft Azure cloud-based, research environment with double authentication where researchers can collaborate using data

that were stored and organised securely. VAC4EU can use this facility through the UMCU tenant. UMCU was responsible for data processing and data security.

9.9 Statistical Methods

9.9.1 Main Summary Measures

Categorical variables were described as the count and proportion of subjects vaccinated with AZD1222 and comparators, by age, sex, region, and prior COVID-19 categories. For continuous variables, mean, standard deviation (SD), median and first and third quartiles (Q1, Q3), and minimum and maximum values were reported.

Incidence rate, prevalence proportion (PP), cumulative incidence, and the 95% CI for each measure were estimated to describe the occurrence of AESIs.

9.9.2 Main Statistical Methods

9.9.2.1 Selection of Study Population

The cohort attrition numbers were reported for the identified subjects receiving a dose of AZD1222 (*all vaccinated population*), then those who had AZD1222 as the first COVID-19 vaccine dose (*all vaccinated first dose population)*, and then unvaccinated subjects after applying the study inclusion/exclusion criteria. Also, the counts and percentages of subjects vaccinated and unvaccinated were reported after matching (*matched population*) (see Section 9.3). The ratio of AZD1222-vaccinated to unvaccinated subjects and the number of times each unvaccinated subject was used as a comparator were reported. Duration of follow-up was described by the mean (SD), median and quartiles 1 and 3, and percentiles 1 and 99. Reasons for censoring among vaccinated and unvaccinated subjects were reported as counts and percentages, overall and by quarter of the index date, to monitor if unvaccinated subjects were censored because they were vaccinated with AZD1222 or another COVID-19 vaccine.

9.9.2.2 Descriptive Analysis of AZD1222 and Other COVID-19 Vaccine Utilisation Patterns Among Those With a First Dose of AZD1222

For the *all vaccinated first dose population*—defined in Section 9.3.2—patterns of second and third COVID-19 vaccine dose over the study period were described with the following measures:

- Number of subjects with at least 1 dose of AZD1222 (total count all vaccinated)
- Number and proportion of subjects with a first dose of AZD1222
- Among those who received a first dose of AZD1222:
  - Number and proportion of subjects who did not receive a second dose of any COVID-19 vaccine

  - Number and proportion of subjects who received a second dose of any COVID-19 vaccine overall and by manufacturer of the second dose (AZ, Pfizer-BioNTech, Moderna, Janssen)
  - Summary of the time (days) between the first and second doses
- Among those who received a first and second dose of AZD1222:
  - Number and proportion of subjects who received a third dose of any COVID-19 vaccine overall and by manufacturer of the third dose (AZ, Pfizer-BioNTech, Moderna, Janssen)
  - Summary of the time (days) between the second and third doses

9.9.2.3 Analysis of Incidence Rates, Prevalence Proportions, and Cumulative Incidence (1 − KM)

As described in Table 5, for the AESIs with **known risk windows** (those for which the end of the risk window is other than 180 or 365 days) and AESIs with **unknown risk windows** (those with a risk window that ends at 180 or 365 days), different analyses were conducted:

- For outcomes that have **known risk windows** (except for anaphylaxis and sudden death), crude IR and 95% CIs were estimated. The crude IR was calculated as the number of subjects with a new AESI during any of the risk windows for dose 1 or 2 divided by the total person-years accumulated during the risk windows after dose 1 and dose 2 (if it was received) in each of the cohorts. For the *all vaccinated population* and the *vaccinated matched cohort* (no repeated subjects), the 95% confidence intervals (CIs) around IR point estimates were computed using the relationship between the Poisson distribution and chi-square distributions as described in Dobson et al [7]. For the *unvaccinated matched cohort* (potentially including repeated subjects), the 95% CIs around IR point estimates were estimated using a generalised estimating equation (GEE) Poisson regression model.
  - For anaphylaxis and sudden death, since time to the event was not of interest, the PPs and 95% CIs were estimated. The crude PP was calculated as the number of subjects with a record of the specific AESI (eg, anaphylaxis or sudden death) during any of the risk windows for dose 1 or 2 divided by the total persons in each cohort. The exact (or Clopper-Pearson) 95% CIs of the PP was estimated. In future reports of the analysis in *matched populations* (which include repeated unvaccinated subjects), the 95% CIs around PP point estimates will be estimated from the GEE Poisson regression model.
- For outcomes that have **unknown risk windows,** cumulative incidence was estimated as 1 − KM, and KM curves and estimates were calculated from the start of the risk window until the end of follow-up. The crude cumulative incidence was estimated for the AESIs with unknown risk windows using the 1 − KM estimator at the last subject not censored,

as all data sources had shorter follow-up than the end of the risk window. Repeated subjects were taken into account to estimate the 95% CI of the unvaccinated matched cohort.

The estimates described above (IR, PP, and 1 − KM) were reported (1) among the *all vaccinated population* before inclusion/exclusion criteria or matching and (2) for the *matched population* in both vaccinated and unvaccinated cohorts. Also, the number of included subjects for each AESI-specific analysis after excluding individuals due to prior history of each AESI was reported. For the AESI TTS, the number of events, person-years, and IR by age category and sex were reported.

To put the study risk estimates in perspective, the publicly available IRs from ACCESS were standardised to the age distribution in each data source [1].

9.9.2.4 Cell Count Restrictions

Cell count restrictions at each research partner are included in Table 6.

Table 6. Small Cell Count Rules in Each Data Source

	CPRD Aurum (UK)	VID (Valencia, Spain)	SIDIAP (Catalonia, Spain)	ARS Toscana (Italy)	PHARMO (Netherlands)
Numbers to be masked	1-4	NA	1-4	NA	1-4-
Text to be used in redactions	< 5	NA	< 5	NA	< 5
Possible to share with UMCU, RTI-HS, DAPs	Yes	NA	Yes	NA	Yes
Possible to share with regulatory authorities. Note: report is provided to authorities by MAH (AstraZeneca)	Yes	NA	Yes	NA	Yes
Comments	A clear statement about cell count suppression is required	No identifiable information may be shared	Not applicable	No identifiable information may be shared	

ARS Toscana, Regional Health Agency of Tuscany; CPRD, Clinical Practice Research Datalink; DAP, data access provider; MAH, marketing authorisation holder; NA, not applicable, PHARMO, PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research; RTI-HS, RTI Health Solutions; SIDIAP, Information System for Research in Primary Care; UK, United Kingdom; UMCU, University Medical Center Utrecht; VID, Valencia Health System Integrated Database.

For any dissemination beyond regulatory authorities, data protection rules regarding small cell count restrictions in Section 9.9.2.4, and Table 6 for redaction of cells with values from 1 to 4.

9.9.3 Missing Values

Subjects with missing values for either age or sex (matching variables) were excluded. Because the underlying data represent attended medical care, it is generally assumed that the absence of information of clinical events or prescriptions/dispensing indicates an absence of the condition or the treatment. Therefore, no missing data were expected for the study variables for interim report 1, including diagnoses. Missing data are expected for some lifestyle or biometric data, such as smoking status or body mass index in primary care electronic medical records, which were not included in analyses for the current interim report. Missing data could have occurred occur for vaccine manufacturer and end of observation period in this interim report 1. If vaccine manufacturer was missing, we used the available vaccine manufacturer from records within 14 days, if any. If there was a missing value for subject location at the end of the observation period, we assumed that the subject was still at the same practice/region at the end of the observation period.

9.9.4 Sensitivity Analyses

No sensitivity analyses were conducted for interim report 1.

9.9.5 Amendments to the Statistical Analysis Plan

The following adjustments to the submitted SAP (Version 1.0, date 30 November 2021) were implemented:

- Subjects were also matched on geographic region as a proxy for socioeconomic status. This was done to align the AZD1222 PASS with other VAC4EU PASS studies, and to facilitate data extraction in data sources where converting into the CDM the whole data was an issue due to size.

9.10 Quality Control

Rigorous quality control (QC) was applied to all deliverables. Data transformation into the CDM was conducted by each DAP in its associated database, with processes as described in Section 9.8. Standard operating procedures or internal process guidance at each research centre were used to guide the conduct of the study. These procedures included rules for secure and confidential data storage, backup, and recovery; methods to maintain and archive project documents; QC procedures for programming; standards for writing analysis plans; and requirements for scientific review by senior staff.

DAP-specific quality-control processes are described in Appendix B 1.

10. RESULTS

For any dissemination beyond regulatory authorities, please refer to the data protection rules regarding small cell count restrictions in Section 9.9.2.4 and Table 6 for redaction of cells with values from 1 to 4.

Data from VID could not be extracted to be included in interim report 1. Data from VID will be analysed as soon as they become available and will be shared with EMA as appropriate.

10.1 Participants

Cohort attrition in all data sources is presented in Table 7 (see also Appendix B 2, Table 4 and Figure 1 for each data source). After applying all eligibility criteria and matching, 4,040,587 vaccinated subjects were included in the AZD1222 cohort in CPRD, 558,566 in SIDIAP, 336,792 in ARS Toscana, and 167,087 in PHARMO. In all data sources, more than 95% of the vaccinated subjects were matched on a 1:5 ratio. Most of the unvaccinated subjects were matched fewer than 3 times. In CPRD, 25% of unvaccinated subjects were matched 5 times or more.

Although data from VID were not included in interim report 1, an evaluation of the actual number of subjects vaccinated with AZD1222 showed that, as of 26 September 2021, VID contained data on 507,846 subjects who had received at least 1 dose of AZD1222 and 469,613 with a second dose (as per the progress report submitted to the EMA on 22 October 2021).

Table 7. Cohort Attrition, Matching Ratio, and Matching Distribution for the *Matched Population*, by Data Source

	CPRD Aurum (UK)	SIDIAP (Catalonia, Spain)	ARS Toscana (Italy)	PHARMO (Netherlands)
AZD1222 cohort				
All vaccinated population	4,171,486	560,744	342,255	168,229
All vaccinated first dose population	4,161,752 (99.77%)	560,712 (99.99%)	342,030 (99.93%)	168,229 (100%)
And with at least 12 months look-back period (eligible to be matched)	4,057,222 (97.49%)	558,568 (99.62%)	336,792 (98.47%)	168,042 (99.89%)
Unique vaccinated subjects not matched	16,635 (0.41%)	[redacted]	0 (0.00%)	955 (0.57%)
Unique vaccinated subjects included after matching	4,040,587 (99.59%)	558,566 (100%)	336,792 (100%)	167,087 (99.43%)
Matching ratio 1:1	19,305 (0.48%)	[redacted]	0 (0%)	1,340 (0.80%)
Matching ratio 1:2	19,689 (0.49%)	[redacted]	1 (< 0.01%)	1,565 (0.94%)
Matching ratio 1:3	19,392 (0.48%)	0 (0%)	0 (0%)	1,615 (0.97%)
Matching ratio 1:4	20,214 (0.50%)	0 (0%)	2 (< 0.01%)	1,663 (1.00%)
Matching ratio 1:5	3,961,987 (98.05%)	[redacted]	336,789 (100%)	160,904 (96.30%)
Unvaccinated cohort				
Unique subjects with no record of vaccination with any COVID-19 vaccine during the study period	12,823,272	5,419,960	3,603,951	2,506,899
And with at least 12 months of look-back time (eligible to be matched)	12,683,746 (98.91%)	5,308,949 (97.95%)	3,415,228 (94.76%)	2,501,869 (99.80%)
Unique unvaccinated subjects matched	5,762,912 (45.44%)	1,128,799 (21.26%)	965,953 (28.28%)	323,940 (12.95%)
Unique unvaccinated subjects not matched	6,920,834 (54.56%)	4,180,150 (78.74%)	2,449,275 (71.72%)	2,177,929 (87.05%)
Non-unique unvaccinated subjects matched	20,007,650	2,792,824	1,683,955	820,487

	CPRD Aurum (UK)	SIDIAP (Catalonia, Spain)	ARS Toscana (Italy)	PHARMO (Netherlands)
Number of times an unvaccinated subject was matched				
Median (Q1, Q3)	2 (1, 5)	1 (1, 3)	1 (1, 2)	1 (1, 3)
Min-Max	1-103	1-22	1-14	1-72
1	2,020,199 (35.06%)	629,657 (55.78%)	577,475 (59.78%)	175,278 (54.11%)
2	1,111,848 (19.29%)	174,798 (15.49%)	210,862 (21.83%)	50,821 (15.69%)
3	691,903 (12.01%)	85,332 (7.56%)	93,229 (9.65%)	29,804 (9.20%)
4	480,640 (8.34%)	59,612 (5.28%)	45,250 (4.68%)	20,432 (6.31%)
5 or more	1,458,322 (25.31%)	179,400 (15.89%))	39,137 (4.05%)	47,605 (14.70%)

ARS Toscana, Regional Health Agency of Tuscany; COVID-19, coronavirus disease 2019; CPRD, Clinical Practice Research Datalink; PHARMO, PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research; Q1, Q3, first and third quartiles; SIDIAP, Information System for Research in Primary Care; UK, United Kingdom.

10.2 Descriptive Data

10.2.1 Description of Age, Sex, Calendar Year, and Prior COVID-19 at the Index Date

Baseline characteristics among the *all vaccinated population* by data source are included in Table 8 (see also Appendix B 2, Table 1.1 for each data source). Overall, CPRD was the data source with the highest number of subjects with at least 1 dose of AZD1222 (4,171,486 subjects), followed by SIDIAP (560,744 subjects), ARS Toscana (342,255 subjects), and PHARMO (168,229 subjects). Although the majority of subjects in CPRD were vaccinated during Q1 2021, in the EU data sources, more subjects were vaccinated during Q2 2021. The age distribution of subjects vaccinated with AZD1222 differed between the UK CPRD and the EU data sources. Subjects in CPRD were younger (median age, 54 years) than subjects in the EU data sources (median age 62 to 69 years). Although in the EU data sources most of the subjects were in the age categories 60 to 69 years and 70 to 79 years, in the CPRD, only 36% of the subjects were aged 60 years or older, and half of the subjects were aged 40 to 59 years. All data sources had a slightly higher proportion of females than males. The median duration of look-back period was 11 years in PHARMO, 15 years in CPRD and in SIDIAP, and 25 years in ARS. Prior history of COVID-19 diagnosis or positive test ranged from 3.21% in ARS Toscana to 12.37% in PHARMO.

Table 8. Distribution of Baseline Characteristics Among the *All Vaccinated Population*, by Data Source

	CPRD (UK)		SIDIAP (Spain)		ARS Toscana (Italy)		PHARMO (Netherlands)	
	N	%[a]	N	%[a]	N	%[a]	N	%[a]
Total subjects	4,171,486	100%	560,744	100%	342,255	100.00%	168,229	100%
Calendar quarter at index date								
Q1 2021	3,461,321	82.98%	216,443	38.60%	142,284	41.57%	39,864	23.70%
Q2 2021	686,535	16.46%	344,301	61.40%	199,358	58.25%	128,365	76.30%
Q3 2021	23,497	0.56%	0	0.00%	613	0.18%	0	0.00%
Q4 2021	133	< 0.01%	0	0.00%	0	0.00%	0	0.00%
Age at index date (years)								
Mean (SD)	54.40	(14.80)	57.75	(11.67)	63.17	(13.64)	59.81	(9.62)
Median (Q1, Q3)	54	(45, 65)	62	(59, 65)	69	(56, 74)	62	(60, 64)
Age group (years)								
0-11	16	< 0.01%	[redacted]	< 0.01%	1	< 0.01%	[redacted]	< 0.01%
12-15	161	< 0.01%	0	0.00%	2	< 0.01%	[redacted]	< 0.01%
16-19	31,096	0.75%	1,967	0.35%	144	0.04%	843	0.50%
20-29	201,817	4.84%	24,973	4.45%	8,397	2.45%	4,181	2.49%
30-39	357,360	8.57%	34,327	6.12%	17,585	5.14%	4,533	2.69%
40-49	943,790	22.62%	49,273	8.79%	36,615	10.70%	6,965	4.14%
50-59	1,144,770	27.44%	59,609	10.63%	37,334	10.91%	13,129	7.80%
60-69	801,556	19.22%	390,465	69.63%	81,767	23.89%	133,799	79.53%
70-79	530,554	12.72%	125	0.02%	160,289	46.83%	2,066	1.23%
80 or more	160,366	3.84%	[redacted]	0.00%	121	0.04%	2,708	1.61%

	CPRD (UK)		SIDIAP (Spain)		ARS Toscana (Italy)		PHARMO (Netherlands)	
	N	%[a]	N	%[a]	N	%[a]	N	%[a]
Sex								
Male	2,038,416	48.87%	254,831	45.45%	153,184	44.76%	80,945	48.12%
Female	2,133,070	51.13%	305,913	54.55%	189,071	55.24%	87,284	51.88%
Duration of look-back period (years)								
Mean (SD)	14.99	(9.23)	14.75	(2.21)	24.94	(10.88)	10.89	(1.56)
Median (Q1, Q3)	15	(6, 26)	15	(15, 15)	25	(17, 33)	11	(11, 11)
COVID-19 history (positive antigen or PCR test or diagnosis)	403,574	9.67%	35,683	6.36%	10,985[b]	3.21%[b]	20,794	12.36%

[a] Percentage unless otherwise specified and in parentheses, eg, SD or Q1, Q3.

[b] In ARS Toscana, COVID-19 history was defined as having a positive PCR (polymerase chain reaction) test or diagnosis.

ARS Toscana, Regional Health Agency of Tuscany; COVID-19, coronavirus disease 2019; CPRD, Clinical Practice Research Datalink; N, number; PCR = polymerase chain reaction; PHARMO, PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research; Q1, Q3, first and third quartiles; SD, standard deviation; SIDIAP, Information System for Research in Primary Care; UK, United Kingdom.

10.2.2 Description of the Follow-up Time and Reasons for Censoring Among Subjects Vaccinated With AZD1222 and Concurrent Unvaccinated Comparators in the *Matched Cohort*

Duration of follow-up by data source is described in Table 9 (see also Appendix B 2, Table 5 for each data source) Among subjects in the AZD1222 cohort, the longest duration of follow-up was observed in CPRD (median follow-up, 7.1 months), followed by ARS Toscana (median follow-up, 4.9 months). The duration of follow-up in SIDIAP and PHARMO was shorter (median follow-up, 2.8 months and 2.3 months, respectively). The duration of follow-up among subjects in the unvaccinated cohort was shorter than among subjects in the AZD1222 cohort, with a median follow-up of less than 2 months in all data sources.

Table 9. Person-Months of Follow-Up in Subjects Vaccinated With AZD1222 and Concurrent Unvaccinated Comparators in the *Matched Population*, by Data Source

	CPRD, UK		SIDIAP, Catalonia, Spain	
	AZD1222 cohort	**Unvaccinated cohort**	**AZD1222 cohort**	**Unvaccinated cohort**
Number of subjects	4,040,587	20,007,650	558,566	2,792,824
Mean (SD)	6.98 (1.32)	2.56 (2.79)	2.75 (0.86)	1.71 (1.36)
Median (Q1, Q3)	7.1 (6.6, 8.0)	1.1 (0.2, 5.2)	2.8 (2.1, 3.2)	1.4 (0.4, 2.8)
P1-P99	1.8-8.9	< 0.1-8.5	0.9-4.6	< 0.1-4.6
	ARS Toscana, Italy		**PHARMO, the Netherlands**	
	AZD1222 cohort	**Unvaccinated cohort**	**AZD1222 cohort**	**Unvaccinated cohort**
Number of subjects	336,792	1,683,955	167,087	820,487
Mean (SD)	4.73 (1.07)	2.17 (1.91)	2.29 (1.03)	1.54 (1.04)
Median (Q1, Q3)	4.9 (4.0, 5.4)	1.4 (0.5, 3.6)	2.3 (1.6, 2.8)	1.4 (0.7, 2.3)
P1-P99	2.7-6.6	< 0.1-6.5	< 0.1-4.2	< 0.1-4.1

ARS Toscana, Regional Health Agency of Tuscany; CPRD, Clinical Practice Research Datalink; PHARMO, PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research; Q1, Q3, first and third quartiles; SD, standard deviation; SIDIAP, Information System for Research in Primary Care; UK, United Kingdom.

The main reasons for censoring are summarised in Table 10 and Figure 5 (see also Appendix B 2, Table 5 and Figures 2 for each data source). Follow-up among subjects in the AZD1222 cohort was censored primarily due to end of the study period. Among subjects in the unvaccinated cohort, the main reason for censoring was receiving a COVID-19 vaccine (either AZD1222 or other).

Table 10. Reasons for Censoring Follow-up Among the *Matched Population*, by Data Source

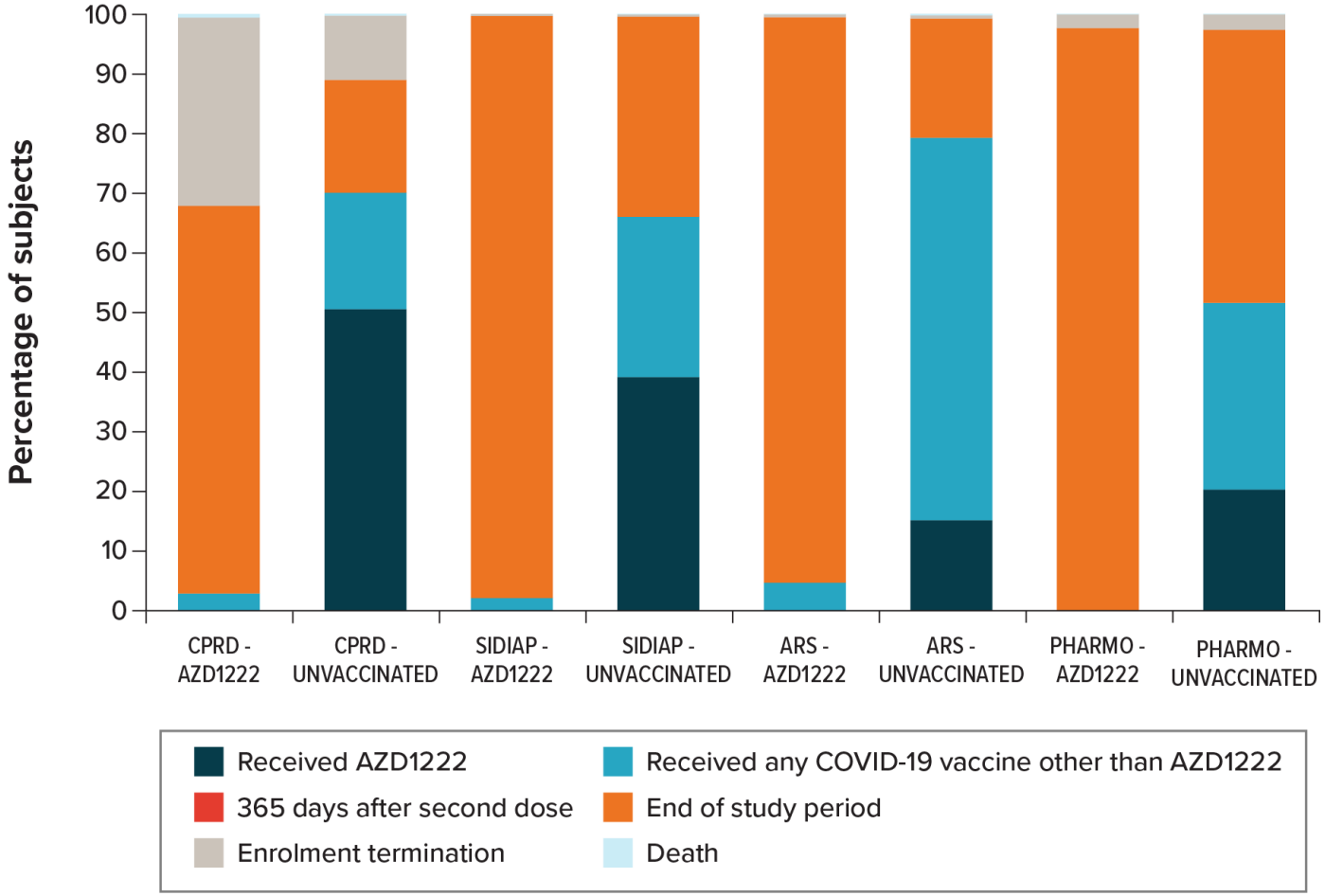
	CPRD, UK		SIDIAP, Catalonia, Spain	
	AZD1222 cohort	**Unvaccinated cohort**	**AZD1222 cohort**	**Unvaccinated cohort**
Number of subjects	4,040,587	20,007,650	558,566	2,792,824
Received AZD1222	0%	50.49%	0%	39.11%
Received any COVID-19 vaccine other than AZD1222	2.88%	19.52%	2.13%	26.89%
Censored 365 days after the second dose of AZD1222	0%	0%	0%	0%
End of study period	64.93%	18.91%	97.51%	33.51%
Enrolment termination date in the health plan or system	31.54%[a]	10.77%[a]	0.33%	0.35%
Death	0.64%	0.32%	0.03%	0.14%
	ARS Toscana, Italy		**PHARMO, Netherlands**	
	AZD1222 cohort	**Unvaccinated cohort**	**AZD1222 cohort**	**Unvaccinated cohort**
Number of subjects	336,792	1,683,955	167,087	820,487
Received AZD1222	0.00%	15.12%	0%	20.26%
Received any COVID-19 vaccine other than AZD1222	4.69%	64.12%	0%[b]	31.31%
Censored 365 days after the second dose of AZD1222	0.00%	0.00%	0%	0%
End of study period	94.72%	19.96%	97.62%	45.74%
Enrolment termination date in the health plan or system	0.49%	0.52%	2.29%	2.60%
Death	0.10%	0.28%	0.09%	0.09%

[a] Enrolment termination date in the health system or database: Please note that for interim report 1, for enrolment termination date in the database, no differentiation was made between whether the last collection date of each general practice represented actual disenrollment from CPRD Aurum or whether it represented an earlier data cut date, prior to 13 October 2021 (latest practice last collection date).

[b] As described in Section 9.4.1.5, the number of subjects vaccinated with AZD1222 is likely underestimated in PHARMO because all doses of COVID-19 vaccines were classified as “unknown” vaccine when heterologous schemes were identified.

ARS Toscana, Regional Health Agency of Tuscany; COVID-19, coronavirus disease 2019; CPRD, Clinical Practice Research Datalink; PHARMO, PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research; SIDIAP, Information System for Research in Primary Care; UK, United Kingdom.

Figure 5. Reasons for Censoring Follow-up Among the *Matched Population*, by Data Source



Note: In CPRD, enrolment termination date in the health system or database: Please note that for interim report 1, for enrolment termination date in the database, no differentiation was made between whether the last collection date of each general practice represented actual disenrollment from CPRD Aurum or whether it represented an earlier data cut date, prior to 13 October 2021 (latest practice last collection date).

ARS (ARS Toscana), Regional Health Agency of Tuscany; COVID-19, coronavirus disease 2019; CPRD, Clinical Practice Research Datalink; PHARMO, PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research; SIDIAP, Information System for Research in Primary Care; UK, United Kingdom.

10.2.3 Descriptive Analysis of AZD1222 and Other COVID-19 Vaccine Utilisation Patterns Among Those With a First Dose of AZD1222 in the *All Vaccinated First Dose Population*

The descriptive analysis of AZD1222 utilisation patterns among those with a first dose of AZD1222 during the study period is summarised in Table 11 (see also Appendix B 2, Table 3 for each data source).

In CPRD, of the 4,161,752 subjects who received AZD1222 as the first dose, 3,857,233 subjects (92.68%) received a second dose of any COVID-19 vaccine. The most common second-dose vaccine was AZD1222 (92.29%). In subjects receiving 2 doses of AZD1222, the mean duration between dose 1 and dose 2 was 10.61 weeks. A total of 105,784 subjects with a first and second dose of AZD1222 (2.75%) received a third dose of a COVID-19 vaccine, which was most frequently Pfizer-BioNTech COVID-19 vaccine.

In SIDIAP, of the 560,712 subjects who received AZD1222 as the first dose, 305,310 subjects (54.45%) received a second dose of any COVID-19 vaccine. The most common second-dose vaccine was AZD1222 (52.31%), followed by Pfizer-BioNTech COVID-19 vaccine (2.13%). In subjects receiving 2 doses of AZD1222, the mean duration between dose 1 and dose 2 was 12.30 weeks. Only [redacted] with a first and second dose of AZD1222 (< 0.01%) received a third dose of a COVID-19 vaccine ([redacted] received AZD1222 as third dose).

In ARS Toscana, of the 342,030 subjects who received AZD1222 as the first dose, 329,892 (96.45%) received a second dose of any COVID-19 vaccine. The most common second-dose vaccine was AZD1222 (91.65%), followed by Pfizer-BioNTech COVID-19 vaccine (4.15%). In subjects receiving 2 doses of AZD1222, the mean duration between dose 1 and dose 2 was 11.92 weeks. A total of 11 subjects with a first and second dose of AZD1222 (< 0.01%) received a third dose of any COVID-19 vaccine.

In PHARMO, of the 168,229 subjects who received AZD1222 as the first dose, 46,693 subjects (27.76%) received a second dose of any COVID-19 vaccine. All second doses captured in the data source were administrations of the AZD1222 vaccine, with a mean duration between dose 1 and dose 2 of 11.31 weeks. No heterologous schemes or third doses were captured in the PHARMO data source due to the conservative systematic approach used during cleaning of the data (see Section 9.4.1.5).

Regarding time between dose 1 and dose 2 of a primary vaccination regime, in all data sources, the majority of vaccinated subjects received the second dose between 9 and 12 weeks after the first dose (see Appendix B 2, Table 3 for each data source).

Table 11. Description of the Utilisation Pattern of Subsequent Doses of a COVID-19 Vaccine in the *All Vaccinated First Dose Population* in the Participating Data Sources During the Overall Study Period (Interim Analysis 1)

	CPRD (UK)		SIDIAP (Spain)		ARS Toscana (Italy)		PHARMO (Netherlands)	
Study period	1 Jan 2021 to 15 Oct 2021		1 Jan 2021 to 30 Jun 2021		1 Feb 2021 to 31 Aug 2021		1 Feb 2021 to 30 Jun 2021	
Subjects with a first dose of AZD1222, n %	4,161,752	100%	560,712	100%	342,030	100%	168,229	100%
Subjects who received only a first dose of AZD1222 by the end of the study period for interim report 1, n %	304,519	7.32%	255,402	45.55%	12,138	3.55%	121,536	72.24%
Subjects with a first dose of AZD1222 who received a second dose of any COVID-19 vaccine, n %	3,857,233	92.68%	305,310	54.45%	329,892	96.45%	46,693	27.76%
AZD1222 as second dose	3,840,711	92.29%	293,335	52.31%	313,454	91.65%	46,693	27.76%
Pfizer-BioNTech COVID-19 vaccine as second dose	15,617	0.38%	11,962	2.13%	14,188	4.15%	0	0%
Moderna COVID-19 vaccine as second dose	[redacted]	0.02%	[redacted]	< 0.01%	2,239	0.65%	0	0%
Janssen COVID-19 vaccine as second dose	[redacted]	< 0.01%	[redacted]	< 0.01%	11	< 0.01%	0	0%
Other COVID-19 vaccine as second dose	0	0%	0	0%	0	0%	0	0%

	CPRD (UK)		SIDIAP (Spain)		ARS Toscana (Italy)		PHARMO (Netherlands)	
Among those with a first dose of AZD1222 who received a second dose of any COVID-19 vaccine, time (weeks) between dose 1 (AZD1222) and dose 2, mean (SD)								
AZD1222	10.61	(1.76)	12.30	(1.54)	11.92	(0.44)	11.31	(1.09)
Pfizer-BioNTech COVID-19 vaccine	15.87	(8.93)	13.59	(2.06)	12.45	(2.50)	0	(0)
Moderna COVID-19 vaccine	11.60	(4.58)	7.31	(3.93)	12.70	(3.11)	0	(0)
Janssen COVID-19 vaccine	22.43	NR	13.14	NR	15.19	(4.12)	0	(0)
Other COVID-19 vaccine	0	(0)	0	(0)	0	(0)	0	(0)
Subjects with a first and second dose of AZD1222 who received a third dose of any COVID-19 vaccine, n %	105,784	2.75%	[redacted]	< 0.01%	11	< 0.01%	0	0%
AZD1222 as third dose	1,616	0.04%	[redacted]	< 0.01%	4	< 0.01%	0	0%
Pfizer-BioNTech COVID-19 vaccine as third dose	104,070	2.71%	[redacted]	0%	5	< 0.01%	0	0%
Moderna COVID-19 vaccine as third dose	[redacted]	0.00%	0	0%	2	< 0.01%	0	0%
Janssen COVID-19 vaccine as third dose	[redacted]	< 0.01%	0	0%	0	0%	0	0%
Other COVID-19 vaccine as third dose	0	0%	0	0%	0	0%	0	0%

	CPRD (UK)		SIDIAP (Spain)		ARS Toscana (Italy)		PHARMO (Netherlands)	
Among those with a first and second dose of AZD1222 who received a third dose of any COVID-19 vaccine, time (weeks) between dose 2 (AZD1222) and dose 3, mean (SD)								
AZD1222	10.82	(7.69)	7.00	(0.61)	5.36	(2.34)	0	(0)
Pfizer-BioNTech COVID-19 vaccine	26.23	(2.28)	0	(0)	6.89	(5.75)	0	(0)
Moderna COVID-19 vaccine	21.45	(7.37)	0	(0)	7.64	(6.36)	0	(0)
Janssen COVID-19 vaccine	4.00	(0)	0	(0)	0	(0)	0	(0)
Other COVID-19 vaccine	0	(0)	0	(0)	0	(0)	0	(0)

ARS Toscana, Regional Health Agency of Tuscany; COVID-19, coronavirus disease 2019; CPRD, Clinical Practice Research Datalink; NR, not reported; PHARMO, PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research; SD, standard deviation; SIDIAP, Information System for Research in Primary Care; UK, United Kingdom.

10.3 Outcome Data

The number of events of each AESI in the *all vaccinated population* and in the *matched population* are summarised in Section 10.4. Complete results are presented in Appendix B 2, Table 2 and Table 11 for each data source.

In all data sources, very few subjects (< 0.50%) were excluded from each AESI-specific analysis in both AZD1222 vaccinated and comparator groups. More subjects were excluded from 3 AESI-specific analyses: vaccine-associated enhanced disease (only the unvaccinated cohort for all data sources), fibromyalgia (both cohorts in CPRD and SIDIAP), and chronic fatigue syndrome/myalgic encephalitis (ME)/postviral fatigue syndrome (PVFS) (both cohorts in CPRD and in ARS Toscana), for which the risk window started at 14, 91 and 183 days, respectively.

10.4 Main Results

10.4.1 Crude Incidence Rates, Prevalence Proportions, and Cumulative Incidence (1 − KM) of AESIs in the *All Vaccinated Population*

Risk estimates for each AESI among all vaccinated population are presented in Appendix B 2, Table 2 for each data source. Overall, the risk estimates obtained were almost identical to those observed for the matched vaccinated population (see Section 10.4.2).

10.4.1.1 Cumulative Incidence of TTS by Age Group and Sex

10.4.1.1.1 CPRD, UNITED KINGDOM

In CPRD, a total of 16 TTS events were identified, of which 9 occurred in males and 7 in females (Table 12). The age group with the highest number of events was 40 to 49 years (5 events), followed by 20 to 29 years ([redacted], and 50 to 59 years and 60 to 69 years ([redacted]). See Appendix B 2, CPRD results, Table 2, TTS.

Table 12. Cumulative Incidence (1 − KM) (95% CI) per 10,000 Subjects of TTS in the *All Vaccinated Population* by Age Group and Sex, CPRD (UK)

	No. of Subjects	No. of Outcomes	Person-Years	1 – KM (95% CI) per 10,000 Subjects	
Overall	4,166,842	16	916,536.7	0.17	(0.10-0.28)
By age group (years)					
0-11	16	0	2.3	0.00	(0.00-1,854.50)
12-15	161	0	32.3	0.00	(0.00-928.79)
16-19	31,068	0	6,772.0	0.00	(0.00-77.04)
20-29	201,254	[redacted]	[redacted]	0.20	(< 0.01-30.47)
30-39	356,597	[redacted]	[redacted]	0.03	(< 0.01-22.77)
40-49	942,493	5	206,401.1	0.05	(< 0.01-14.04)
50-59	1,143,755	[redacted]	[redacted]	0.03	(< 0.01-12.73)
60-69	801,065	[redacted]	[redacted]	0.04	(< 0.01-15.21)
70-79	530,327	0	115,621.4	0.00	(0.00-18.65)
80 or more	160,106	0	34,100.2	0.00	(0.00-33.94)
By sex					
Male	2,035,710	9	447,818.6	0.04	(< 0.01-9.56)
Female	2,131,079	7	468,706.5	0.03	(< 0.01-9.34)

Note: A total of 53 subjects had “unknown” value for sex.

CI, confidence interval; CPRD, Clinical Practice Research Datalink; KM, Kaplan-Meier; TTS, thrombosis with thrombocytopaenia syndrome; UK, United Kingdom.

10.4.1.1.2 SIDIAP, CATALONIA, SPAIN

In SIDIAP, 5 TTS events were identified, [redacted] in males and [redacted] in females. By age group, [redacted] were found in subjects aged 40 to 49 years, [redacted] among subjects aged 50 to 59 years, and [redacted] among subjects aged 60 to 69 years (Table 13). See Appendix B 2, SIDIAP results, Table 2, TTS.

Table 13. Cumulative Incidence (1 − KM) (95% CI) per 10,000 Subjects of TTS in the *All Vaccinated Population* by Age Group and Sex, SIDIAP (Catalonia, Spain)

	No. of Subjects	No. of Outcomes	Person-Years	1 − KM (95% CI) per 10,000 Subjects	
Overall	559,441	5	75,001.6	0.67	(0.22-1.56)
By age group (years)					
0-11	[redacted]	0	[redacted]	0.00	(0.00-5245.32)
12-15	0	NA	NA	NA	NA
16-19	1,963	0	314.3	0.00	(0.00-306.53)
20-29	24,895	0	4,202.1	0.00	(0.00-82.09)
30-39	34,148	0	5,851.2	0.00	(0.00-70.10)
40-49	48,980	[redacted]	[redacted]	0.41	(< 0.01-61.11)
50-59	59,434	[redacted]	[redacted]	0.17	(< 0.01-55.65)
60-69	389,894	[redacted]	[redacted]	0.05	(< 0.01-21.80)
70-79	122	0	11.0	0.00	(0.00-1202.22)
80 or more	[redacted]	0	[redacted]	0.00	(0.00-4588.78)
By sex					
Male	254,276	[redacted]	[redacted]	0.12	(< 0.01-27.05)
Female	305,165	[redacted]	[redacted]	0.07	(< 0.01-24.64)

CI, confidence interval; KM, Kaplan-Meier; NA, not available; SIDIAP, Information System for Research in Primary Care; TTS, thrombosis with thrombocytopaenia syndrome.

10.4.1.1.3 ARS TOSCANA, TUSCANY, ITALY

In ARS Toscana, 2 events of TTS were identified, both 2 females, 1 each aged 50 to 59 years and 70 to 79 years (Table 14). See Appendix B 2, ARS Toscana results, Table 2, TTS.

Table 14. Cumulative Incidence (1 − KM) (95% CI) per 10,000 Subjects of TTS in the *All Vaccinated Population* by Age Group and Sex, ARS Toscana (Italy)

	No. of Subjects	No. of Outcomes	Person-Years	1 − KM (95% CI) per 10,000 Subjects	
Overall	340,774	2	71,472.9	0.28	(0.03-1.01)
By age group (years)					
0-11	1	0	0.1	0.00	(0.00-6,825.00)
12-15	2	0	0.1	0.00	(0.00-5,245.32)
16-19	144	0	22.3	0.00	(0.00-803.25)
20-29	8,218	0	1,691.5	0.00	(0.00-149.81)
30-39	17,303	0	3,646.2	0.00	(0.00-95.82)
40-49	36,353	0	7,253.6	0.00	(0.00-71.11)
50-59	37,173	1	7,599.8	0.27	(< 0.01-70.64)
60-69	81,467	0	15,572.9	0.00	(0.00-47.58)
70-79	159,993	1	35,661.4	0.06	(< 0.01-34.02)
80 or more	120	0	24.9	0.00	(0.00-1,057.20)
By sex					
Male	152,355	0	31,618.5	0.00	(0.00-34.79)
Female	188,419	2	39,854.4	0.11	(< 0.01-31.39)

ARS Toscana = Regional Health Agency of Tuscany; CI, confidence interval; KM, Kaplan-Meier; PY, person-years; TTS, thrombosis with thrombocytopaenia syndrome.

10.4.1.1.4 PHARMO, NETHERLANDS

No events of TTS were identified in PHARMO (Table 15) (see also Appendix B 2, PHARMO results, Table 2, TTS).

Table 15. Cumulative Incidence (1 − KM) (95% CI) per 10,000 Subjects of TTS in the *All Vaccinated Population* by Age Group and Sex, PHARMO (Netherlands)

	No. of Subjects	No. of Outcomes	Person-Years	1 − KM (95% CI) per 10,000 Subjects	
Overall	166,908	0	20,769.8	0.00	(0.00-1.78)
By age group (years)					
0-11	[redacted]	0	[redacted]	0.00	(0.00-4,282.78)
12-15	[redacted]	0	[redacted]	0.00	(0.00-5,245.32)
16-19	839	0	101.0	0.00	(0.00-419.53)
20-29	4,159	0	499.1	0.00	(0.00-210.39)
30-39	4,504	0	546.9	0.00	(0.00-202.17)
40-49	6,915	0	870.2	0.00	(0.00-163.23)
50-59	13,045	0	1,646.8	0.00	(0.00-118.91)
60-69	132,701	0	16,597.1	0.00	(0.00-37.28)
70-79	2,052	0	227.7	0.00	(0.00-291.64)
80 or more	2,688	0	280.4	0.00	(0.00-214.54)
By sex					
Male	80,280	0	9,990.2	0.00	(0.00-47.93)
Female	86,625	0	10,779.1	0.00	(0.00-46.14)

CI, confidence interval; KM, Kaplan-Meier; PHARMO, PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research; TTS, thrombosis with thrombocytopaenia syndrome.

Note: A total of 3 subjects had "unknown" value for sex.

10.4.2 Crude Incidence Rates, Prevalence Proportions, and Cumulative Incidence (1 − KM) of AESIs in the *Matched Population*

Crude risk estimates for individual AESI in the matched cohorts, based on definition and duration of risk windows are presented in Table 16 (see also Appendix B 2, Table 11 for each data source). The Kaplan-Meier (KM) figures for AESIs with unknown risk window can be found in Appendix B 2, Figures 5 for each data source. Additionally, crude risk estimates for individual AESIs in the matched cohorts and risk estimates published in the ACCESS project standardised to the age distribution of each data source are included in Figure 6 (known risk windows) and Figure 7 (unknown risk windows) [1]. A table presenting the ACCESS project risk estimates standardised to the age distribution of each data source in this study can be found in Appendix B 3.

Table 16. Crude Risk Estimates for AESIs in the *Matched Cohorts* With Default Risk Windows

AESI (Risk Window)	CPRD, UK		SIDIAP, Catalonia, Spain		ARS Toscana, Italy		PHARMO, Netherlands	
	No. of events	Risk (95% CI) per 10,000	No. of events	Risk (95% CI) per 10,000	No. of events	Risk (95% CI) per 10,000	No. of events	Risk (95% CI) per 10,000
AESIs with known risk window[a]								
Thrombosis without thrombocytopaenia (1-42)								
AZD1222	22	0.25 (0.15-0.37)	[redacted]	0.13 (0.00-0.75)	2	0.28 (0.03-1.02)	0	0.00 (0.00-1.79)
Unvaccinated	27	0.13 (0.05-0.31)	[redacted]	0.08 (0.02-0.32)	4	0.21 (0.03-1.52)	0	NR[d]
Thrombosis with thrombocytopaenia syndrome (1-42)								
AZD1222	15	0.17 (0.09-0.28)	5	0.67 (0.22-1.56)	2	0.28 (0.03-1.02)	0	0.00 (0.00-1.79)
Unvaccinated	[redacted]	0.01 (0.00-0.04)	5	0.20 (0.05-0.73)	7	0.37 (0.10-1.35)	0	NR[d]
Thrombocytopenia with associated bleeding (1-42)								
AZD1222	6	0.07 (0.02-0.15)	5	0.67 (0.22-1.56)	1	0.14 (0.00-0.79)	0	0.00 (0.00-1.79)
Unvaccinated	[redacted]	0.01 (0.00-0.04)	7	0.28 (0.10-0.76)	10	0.53 (0.19-1.51)	0	NR[d]
Thrombocytopaenia (1-42)								
AZD1222	604	6.79 (6.26-7.36)	118	15.81 (13.08-18.93)	11	1.56 (0.78-2.78)	5	2.42 (0.79-5.65)
Unvaccinated	1,034	4.90 (4.23-5.67)	558	22.18 (18.52-26.55)	91	4.87 (3.42-6.93)	13	1.74 (0.66-4.56)
Narcolepsy (1-42)								
AZD1222	23	0.26 (0.16-0.39)	[redacted]	0.27 (0.03-0.97)	0	0.00 (0.00-0.52)	0	0.00 (0.00-1.79)
Unvaccinated	59	0.28 (0.15-0.53)	7	0.28(0.08-1.00)	0	NR	0	NR[d]
Acute aseptic arthritis (1-42)								
AZD1222	7,680	87.20 (85.26-89.18)	374	50.25 (45.28-55.61)	52	7.36 (5.50-9.65)	5	2.42 (0.79-5.65)
Unvaccinated	8,811	42.24 (40.12-44.47)	915	36.51 (32.07-41.56)	131	7.01 (5.48-8.97)	27	3.61 (1.74-7.48)
Guillain-Barré syndrome (1-42)								
AZD1222	41	0.46 (0.33-0.63)	9	1.20 (0.55-2.29)	2	0.28 (0.03-1.02)	0	0.00 (0.00-1.79)
Unvaccinated	48	0.23 (0.12-0.42)	20	0.79 (0.28-2.24)	8	0.43 (0.14-1.28)	[redacted]	0.40 (0.06-2.84)

AESI (Risk Window)	CPRD, UK		SIDIAP, Catalonia, Spain		ARS Toscana, Italy		PHARMO, Netherlands	
	No. of events	Risk (95% CI) per 10,000	No. of events	Risk (95% CI) per 10,000	No. of events	Risk (95% CI) per 10,000	No. of events	Risk (95% CI) per 10,000
Postural orthostatic tachycardia syndrome (1-42)								
AZD1222	55	0.62 (0.47-0.80)	NA		NA		NA	
Unvaccinated	78	0.37 (0.25-0.54)	NA		NA		NA	
Acute cardiac injury including microangiopathy, cardiogenic shock, heart failure (1-90)								
AZD1222	7,096	41.10 (40.15-42.07)	312	25.04 (22.33-27.97)	350	27.21 (24.44-30.22)	66	21.05 (16.28-26.78)
Unvaccinated	8,306	23.64 (22.24-25.13)	1,165	30.82 (26.90-35.31)	1,816	61.71 (56.83-67.01)	181	17.43 (12.04-25.23)
Stress cardiomyopathy (1-42)								
AZD1222	44	0.49 (0.36-0.66)	6	0.80 (0.29-1.75)	5	0.71 (0.23-1.65)	0	0.00 (0.00-1.79)
Unvaccinated	43	0.20 (0.10-0.41)	[redacted]	0.16 (0.03-0.75)	15	0.80 (0.43-1.50)	[redacted]	0.13 (0.02-0.95)
Myocardial infarction (1-28)								
AZD1222	1,295	21.85 (20.67-23.07)	100	18.77 (15.27-22.82)	109	22.51 (18.49-27.16)	6	4.12 (1.51-8.97)
Unvaccinated	2,836	18.71 (17.13-20.45)	449	23.54 (19.86-27.89)	421	30.45 (26.58-34.88)	52	9.36 (2.54-34.46)
Myocarditis/pericarditis (1-42)								
AZD1222	180	2.02 (1.74-2.34)	18	2.41 (1.43-3.81)	47	6.65 (4.89-8.85)	0	0.00 (0.00-1.79)
Unvaccinated	335	1.59 (1.27-1.98)	73	2.90 (1.86-4.51)	337	18.06 (15.18-21.48)	[redacted]	0.13 (0.02-0.95)
Acute kidney injury (1-14)								
AZD1222	949	32.02 (30.01-34.12)	70	24.33 (18.96-30.73)	23	9.34 (5.92-14.01)	35	46.06 (32.08-64.06)
Unvaccinated	2,539	29.98 (27.66-32.50)	411	37.47 (32.06-43.80)	273	35.40 (30.18-41.54)	96	31.32 (22.34-43.92)
Acute liver injury (1-14)								
AZD1222	60	2.02 (1.54-2.60)	7	2.43 (0.98-5.00)	4	1.62 (0.44-4.16)	0	0.00 (0.00-4.84)
Unvaccinated	183	2.15 (1.57-2.95)	112	10.17 (7.61-13.58)	16	2.07 (1.17-3.68)	[redacted]	0.32 (0.05-2.30)

AESI (Risk Window)	CPRD, UK		SIDIAP, Catalonia, Spain		ARS Toscana, Italy		PHARMO, Netherlands	
	No. of events	Risk (95% CI) per 10,000	No. of events	Risk (95% CI) per 10,000	No. of events	Risk (95% CI) per 10,000	No. of events	Risk (95% CI) per 10,000
Transverse myelitis (1-90)								
AZD1222	47	0.27 (0.20-0.36)	0	0.00 (0.00-0.30)	2	0.16 (0.02-0.56)	0	0.00 (0.00-1.17)
Unvaccinated	62	0.18 (0.10-0.32)	[redacted]	0.03 (0.00-0.19)	3	0.10 (0.02-0.44)	0	NR[d]
Encephalitis (including acute disseminated encephalomyelitis) (1-42)								
AZD1222	42	0.47 (0.34-0.64)	6	0.80 (0.29-1.75)	4	0.57 (0.15-1.45)	[redacted]	1.94 (0.53-4.96)
Unvaccinated	61	0.29 (0.17-0.49)	17	0.67 (0.24-1.90)	14	0.75 (0.38-1.49)	[redacted]	0.13 (0.02-0.95)
Other peripheral and polyneuropathies (1-42)								
AZD1222	474	5.33 (4.86-5.83)	78	10.45 (8.26-13.04)	9	1.27 (0.58-2.42)	NA	
Unvaccinated	556	2.64 (2.15-3.24)	292	11.60 (9.35-14.39)	43	2.30 (1.39-3.80)	NA	
Generalised convulsions (0-14)								
AZD1222	495	15.55 (14.21-16.98)	32	10.28 (7.03-14.51)	15	5.68 (3.18-9.37)	[redacted]	1.22 (0.03-6.78)
Unvaccinated	1,077	11.68 (10.39-13.12)	141	11.79 (9.23-15.05)	133	15.97 (12.66-20.15)	[redacted]	0.89 (0.29-2.77)
Optic neuritis/neuromyelitis optica spectrum disorder (1-42)								
AZD1222	49	0.55 (0.41-0.73)	9	1.20 (0.55-2.29)	2	0.28 (0.03-1.02)	NA	
Unvaccinated	110	0.52 (0.34-0.80)	19	0.75 (0.32-1.80)	6	0.32 (0.13-0.81)	NA	
Bell's palsy (1-42)								
AZD1222	484	5.44 (4.97-5.95)	74	9.91 (7.78-12.44)	18	2.55 (1.51-4.02)	34	16.48 (11.41-23.03)
Unvaccinated	778	3.69 (3.18-4.28)	300	11.92 (9.41-15.09)	56	3.00 (2.04-4.41)	132	17.66 (12.02-25.94)
Anaphylaxis[b] (0-2)								
AZD1222	66	0.16 (0.13-0.21)	6	0.11 (0.04-0.23)	2	0.06 (0.01-0.21)	39	2.34 (1.67-3.20)
Unvaccinated	153	0.08 (0.06-0.09)	7	0.03 (0.01-0.05)	0	0.00 (0.00-0.02)	86	1.06 (0.84-1.30)

AESI (Risk Window)	CPRD, UK		SIDIAP, Catalonia, Spain		ARS Toscana, Italy		PHARMO, Netherlands	
	No. of events	Risk (95% CI) per 10,000	No. of events	Risk (95% CI) per 10,000	No. of events	Risk (95% CI) per 10,000	No. of events	Risk (95% CI) per 10,000
Rhabdomyolysis (1-42)								
AZD1222	84	0.94 (0.75-1.17)	6	0.80 (0.29-1.75)	3	0.42 (0.09-1.24)	[redacted]	0.97 (0.12-3.50)
Unvaccinated	176	0.83 (0.60-1.16)	35	1.39 (0.61-3.15)	37	1.98 (1.14-3.42)	0	NR[d]
Multisystem inflammatory syndrome in adults/children (1-42)								
AZD1222	0	0.00 (0.00-0.04)	[redacted]	0.27 (0.03-0.97)	NA		0	0.00 (0.00-1.79)
Unvaccinated	0	NR[d]	[redacted]	0.08 (0.02-0.32)	NA		0	NR[d]
Sudden death[b] (0-6)								
AZD1222	[redacted]	0.00 (0.00-0.01)	0	0.00 (0.00-0.07)	0	0.00 (0.00-0.11)	[redacted]	0.18 (0.04-0.52)
Unvaccinated	[redacted]	0.00 (0.00-0.00)	0	0.00 (0.00-0.01)	1	0.01 (0.00-0.03)	48	0.59 (0.43-0.78)
ARDS (1-28)								
AZD1222	53	0.89 (0.67-1.17)	22	4.12 (2.58-6.24)	6	1.24 (0.45-2.69)	[redacted]	1.37 (0.17-4.96)
Unvaccinated	185	1.22 (0.88-1.69)	199	10.41 (7.97-13.59)	105	7.57 (5.60-10.24)	[redacted]	0.18 (0.03-1.28)
AESIs with unknown risk window[c]								
Myasthenia gravis (1-365)								
AZD1222	201	0.69 (0.00-6.73)	11	0.29 (0.00-14.49)	4	0.12 (0.00-22.44)	NA	
Unvaccinated	129	0.17 (0.00-2.89)	21	0.16 (0.00-6.33)	10	0.14 (0.00-10.12)	NA	
Autoimmune thyroiditis (1-180)								
AZD1222	899	2.53 (0.00-8.58)	74	2.15 (0.00-16.35)	146	6.69 (0.00-28.87)	[redacted]	0.08 (0.01-27.98)
Unvaccinated	1,571	4.53 (0.00-9.73)	238	2.09 (0.00-8.27)	490	8.71 (0.00-18.75)	0	0.00 (0.00-11.41)
Capillary leak syndrome (1-365)								
AZD1222	[redacted]	0.00 (0.00-6.05)	NA		NA		NA	
Unvaccinated	0	0.00 (0.00-2.72)	NA		NA		NA	

AESI (Risk Window)	CPRD, UK		SIDIAP, Catalonia, Spain		ARS Toscana, Italy		PHARMO, Netherlands	
	No. of events	Risk (95% CI) per 10,000	No. of events	Risk (95% CI) per 10,000	No. of events	Risk (95% CI) per 10,000	No. of events	Risk (95% CI) per 10,000
Acute pancreatitis (1-365)								
AZD1222	1,609	5.15 (0.00-11.21)	79	1.80 (0.00-16.00)	80	2.86 (0.00-25.19)	[redacted]	0.15 (0.00-28.05)
Unvaccinated	2,090	3.35 (0.60-6.10)	290	2.11 (0.00-8.29)	173	2.39 (0.00-12.39)	8	0.10 (0.00-11.51)
Multiple sclerosis, and other demyelinating disorders (1-365)								
AZD1222	1,310	3.83 (0.00-9.88)	19	0.70 (0.00-14.89)	16	0.57 (0.00-22.89)	[redacted]	0.48 (0.00-28.38)
Unvaccinated	1,484	2.73 (0.00-5.53)	110	0.94 (0.00-7.11)	100	2.05 (0.00-12.04)	10	0.15 (0.00-11.56)
Fibromyalgia (91-365)								
AZD1222	768	8.74 (1.11-16.38)	68	8.91 (0.00-40.86)	NA		NA	
Unvaccinated	1,006	5.06 (0.00-10.40)	235	8.92 (0.00-24.71)	NA		NA	
Chronic fatigue syndrome/ME/PVFS (183-365)								
AZD1222	5	0.56 (0.00-22.74)	NA		0	0.00 (0.00-316.59)	NA	
Unvaccinated	[redacted]	0.70 (0.00-18.30)	NA		0	0.00 (0.00-238.49)	NA	
Anosmia, ageusia (1-365)								
AZD1222	2,334	7.81 (1.74-13.88)	59	2.12 (0.00-16.35)	0	0.00 (0.00-22.32)	11	1.18 (0.00-29.09)
Unvaccinated	4,118	9.60 (3.48-15.72)	201	2.03 (0.00-8.22)	0	0.00 (0.00-9.98)	62	1.59 (0.00-13.02)
Type III hypersensitivity reactions (1-365)								
AZD1222	5,654	19.71 (13.29-26.13)	131	2.94 (0.00-17.14)	69	2.57 (0.00-24.90)	NA	
Unvaccinated	4,959	7.75 (5.01-10.49)	437	3.31 (0.00-9.50)	499	6.18 (0.00-16.18)	NA	
Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease, including ARDS (14-365)								
AZD1222	0	0.00 (0.00-4.11)	32	0.71 (0.00-19.01)	20	0.64 (0.00-18.93)	[redacted]	0.19 (0.00-34.08)
Unvaccinated	0	0.00 (0.00-2.21)	178	1.25 (0.00-10.67)	146	2.15 (0.00-11.34)	[redacted]	0.04 (0.00-16.57)

AESI (Risk Window)	CPRD, UK		SIDIAP, Catalonia, Spain		ARS Toscana, Italy		PHARMO, Netherlands	
	No. of events	Risk (95% CI) per 10,000	No. of events	Risk (95% CI) per 10,000	No. of events	Risk (95% CI) per 10,000	No. of events	Risk (95% CI) per 10,000
Erythema multiforme (1-365)								
AZD1222	95	0.31 (0.00-6.35)	8	0.18 (0.00-14.37)	12	0.43 (0.00-22.75)	[redacted]	0.06 (0.00-27.96)
Unvaccinated	117	0.20 (0.00-2.92)	29	0.25 (0.00-6.42)	20	0.26 (0.00-10.24)	0	0.00 (0.00-11.41)
Chilblain-like skin lesions (1-365)								
AZD1222	386	1.01 (0.00-7.05)	17	0.44 (0.00-14.63)	1	0.03 (0.00-22.35)	[redacted]	0.19 (0.00-28.09)
Unvaccinated	679	0.58 (0.00-3.30)	91	0.59 (0.00-6.76)	0	0.00 (0.00-9.98)	20	0.37 (0.00-11.79)

[a] Incidence rate per 10,000 person-years, for outcomes with known risk windows.

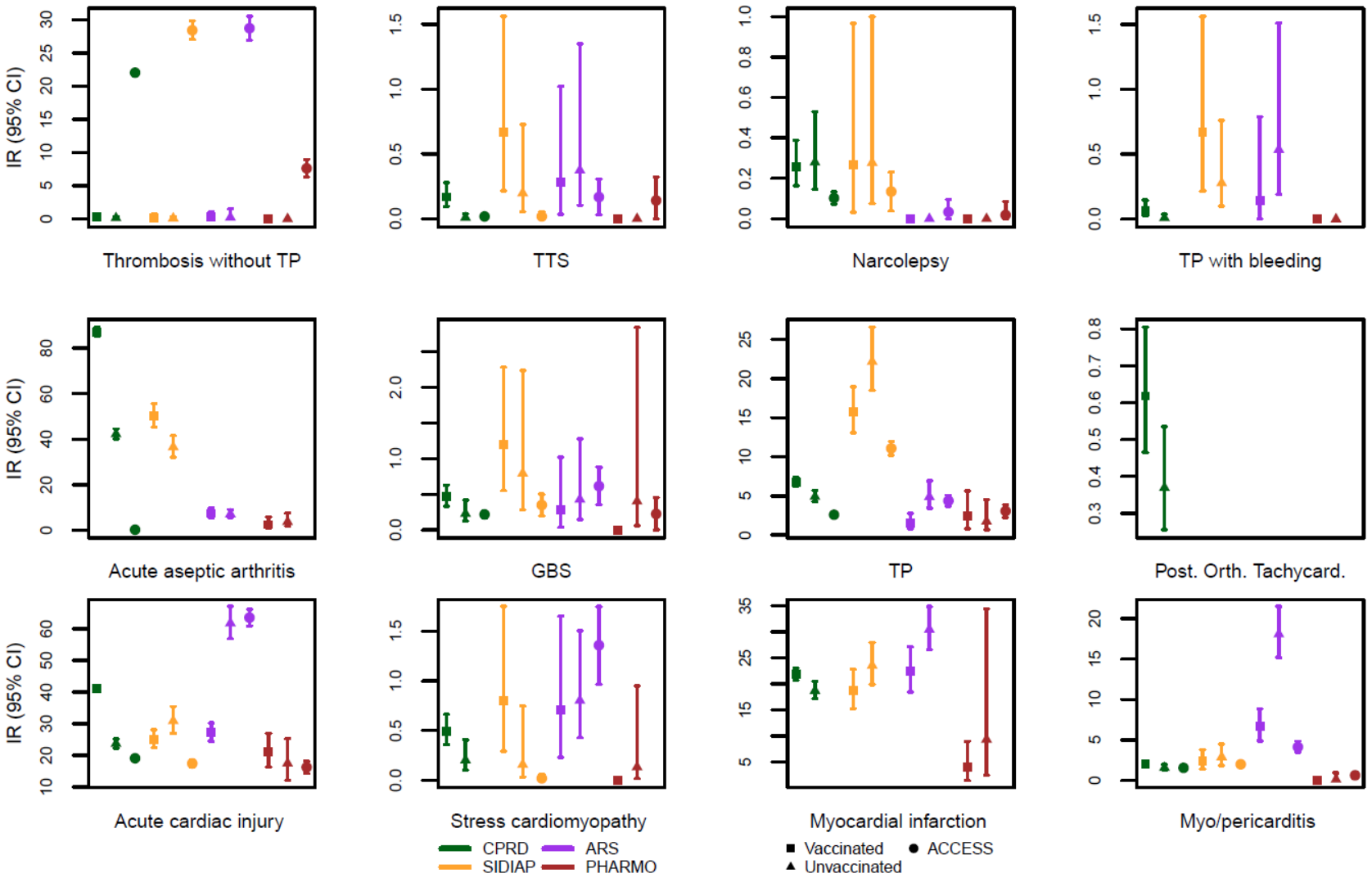
[b] Prevalence proportion per 10,000 subjects, for outcomes with known risk windows and very short risk windows.

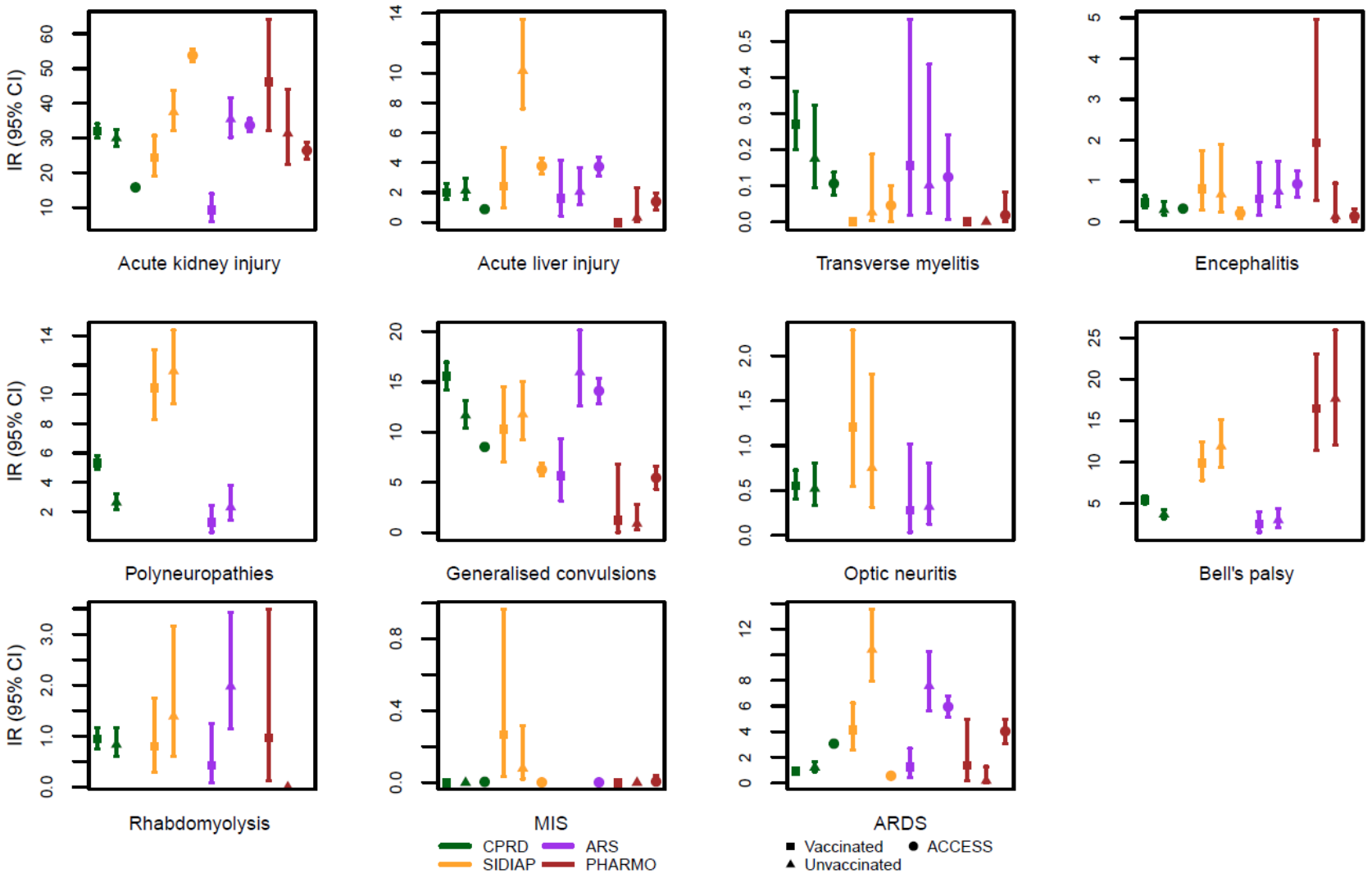
[c] 1 – KM cumulative incidence per 10,000 subjects, for outcomes with unknown risk windows.

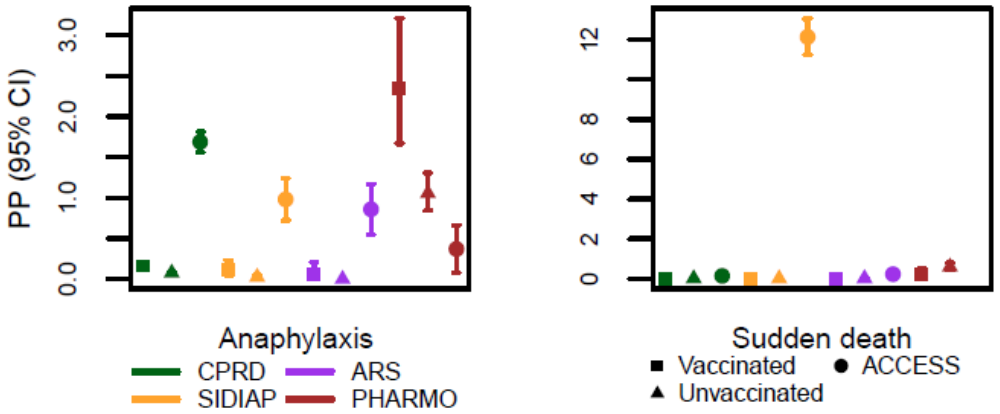
[d] When there are 0 events, the 95% confidence intervals of the incidence rates cannot be estimated using GEE models.

AESI, adverse event of special interest; ARDS, acute respiratory distress syndrome; ARS Toscana, Regional Health Agency of Tuscany; CI, confidence interval; CPRD, Clinical Practice Research Datalink; GEE, generalised estimating equation; KM, Kaplan-Meier; ME, myalgic encephalitis; NA, not available; NR, not reportable; PHARMO, PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research; PVFS, postviral fatigue syndrome; SIDIAP, Information System for Research in Primary Care; UK, United Kingdom.

Figure 6. Crude Risk Estimates Within the Default Risk Windows in the *Matched Cohorts* and Age-Standardised Risk Estimates From the ACCESS Project, for AESIs With Known Risk Windows, by Data Source




IR (95% CI)
Acute kidney injury
Acute liver injury
Transverse myelitis
Encephalitis
Polyneuropathies
Generalised convulsions
Optic neuritis
Bell's palsy
Rhabdomyolysis
MIS
CPRD
ARS
SIDIAP
PHARMO
ARDS
Vaccinated
ACCESS
Unvaccinated

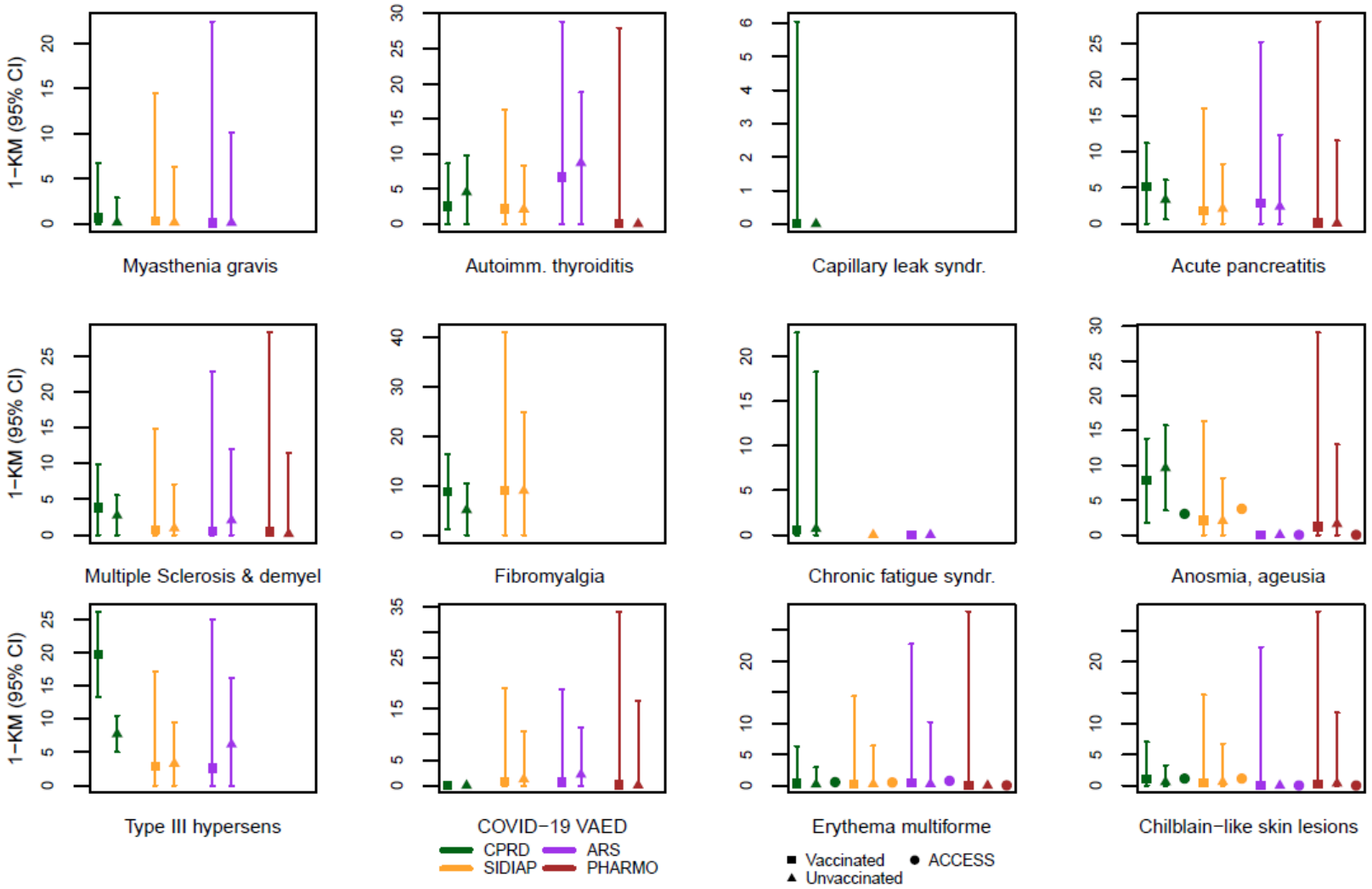


Note: When there were 0 events, this information has been included in the figure as a dot. However, the corresponding 95% CIs have not been plotted. Incidence rates of AESIs estimated in the ACCESS project [1] were standardised to the age distribution in each data source included in interim analysis 1.

Because the ACCESS project did not have some of the composite AESIs, and instead these were reported separately, or only 1 of the components of the composite AESI was available, the figures include the component that was more frequent. For thrombosis with or without thrombocytopaenia, data on venous thromboembolism with or without thrombocytopaenia from ACCESS have been included. For ACI, data on the standardised IR of heart failure, and not on microangiopathy or cardiogenic shock, have been included from ACCESS. For encephalitis, data on meningoencephalitis and not on ADEM have been included.

ACI, acute cardiac injury; ADEM, acute disseminated encephalomyelitis; AESI, adverse event of special interest; ARDS, acute respiratory distress syndrome; ARS (ARS Toscana), Regional Health Agency of Tuscany; CI, confidence interval; CPRD, Clinical Practice Research Datalink; GBS, Guillain-Barré syndrome; IR, incidence rate; Myo/pericarditis, myocarditis/pericarditis; MIS, multisystem inflammatory syndrome; PHARMO, PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research; Post. Orth. Tachycard, postural orthostatic tachycardia; SIDIAP, Information System for Research in Primary Care; TP, thrombocytopaenia; TTS, thrombosis with thrombocytopaenia syndrome.

Figure 7. Crude Risk Estimates Within the Default Risk Windows in the *Matched Cohorts* and Age-Standardised Risk Estimates From the ACCESS Project, for AESIs With Unknown Risk Windows, by Data Source



Note: Incidence rates of AESIs estimated from the ACCESS project [1] were standardised to the age distribution in each data source included in interim analysis 1.

AESI, adverse event of special interest; ARS (ARS Toscana), Regional Health Agency of Tuscany; Autoimm. Thyroiditis, Autoimmune thyroiditis; CI, confidence interval; COVID-19, coronavirus disease 2019; CPRD, Clinical Practice Research Datalink; KM, Kaplan-Meier; PHARMO, PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research; SIDIAP, Information System for Research in Primary Care; Syndr., Syndrome; VAED, vaccine-associated enhanced disease.

10.5 Other Analyses

None.

10.6 Adverse Events/Adverse Reactions

According to current guidelines from the International Society for Pharmacoepidemiology ISPE [21] and the EMA *Guideline on Good Pharmacovigilance Practices, Module VI* [9], non-interventional studies using secondary data such as those described in this report, conducted using medical chart reviews or electronic claims and healthcare records, do not require expedited reporting of adverse events or adverse reactions.

11. DISCUSSION

For any dissemination beyond regulatory authorities, please refer to the data protection rules regarding small cell count restrictions in Section 9.9.2.4 and Table 6 for redaction of cells with values from 1 to 4.

In accordance with the recommendations of the American Statistical Association, the International Committee for Medical Journal Editors [19], and expert opinion on the misuse of significance testing [15; 26; 31], we avoid relying on statistical significance to interpret study results. Instead of a dichotomous interpretation based on *P* values and significance testing, we rely on a quantitative interpretation that considers the magnitude, precision, and possible bias in the estimates that we derive and report. We believe that this is a more appropriate approach than one that ascribes to chance any result that does not meet conventional criteria for statistical significance.

11.1 Key Results

Interim report 1 aims to provide an initial description of the number of subjects vaccinated with AZD1222 and their vaccination patterns, the number of potential comparators and their follow-up, and an estimate of the IRs of the AESIs of interest. Results about crude incidences should be interpreted with caution and should not be used for benefit-risk assessment at this stage. Also, no comparison between vaccinated and unvaccinated subjects should be formally conducted given the limitations described in Section 11.2 about limited follow-up, lack of adjustment by potential confounding, no standardisation of IRs, and limitations in AESI definitions for the analyses conducted for interim report 1.

Overall, more than 5.2 million subjects were vaccinated with AZD1222, and vaccine coverage was in line with the expected numbers as compared with national/regional data [8; 24]. AZD1222 was most frequently administered to subjects aged 60 to 79 years, except in the UK, where it was administered to a wider age range. In SIDIAP and PHARMO, where the duration of follow-up was shorter for interim report 1, only a first dose could be observed in 45.55%

and 72.24% of the subjects, respectively. In CPRD and in ARS Toscana, where the study period for interim report 1 was longer, 92.68% and 96.45%, respectively, of the subjects who received a first dose of AZD1222 also received a second dose of a COVID-19 vaccine (AZD1222 in 99% and 100% of the subjects, respectively).

Evaluation of the availability of unvaccinated controls showed that there were more than 24.35 million unvaccinated subjects; that more than 99% of the vaccinees (22.5 million) could be matched to unvaccinated subjects; and that for more than 96% of the vaccinated subjects, matching could be done in a 1:5 ratio. Median duration of follow-up ranged from 2.3 to 7.1 months among vaccinated subjects and from 1.1 to 1.4 months among unvaccinated subjects. The main reason for censoring among vaccinated subjects was reaching the end of the study period for interim report 1; among unvaccinated subjects, it was being vaccinated with AZD1222 or another COVID-19 vaccine.

The crude incidence of the AESIs described in Section 10.4 varied across data sources. Some AESIs could not be evaluated due to lack of codes to define these events in some coding systems, and some AESIs had very few or no events. Because very few vaccinated subjects were excluded due to not having 12 months of follow-up, and most of the vaccinated subjects could be matched, there were no major differences in the risk estimates of AESIs among the *all vaccinated population* compared with the matched AZD1222 vaccinated cohort.

A description of the risk estimates of each AESI and a brief reference to background rates reported in other studies is described in the following subsections (see description of the main design and countries and data sources included in these studies in Section 11.3.4, see standardised IRs from the pre-pandemic period from the ACCESS project [general population] in Figure 6, Figure 7, and Appendix B 2).

11.1.1 AESIs With Known Risk Windows (Risk Window Less Than 180 Days)

Thrombosis With Thrombocytopaenia Syndrome (Risk Window: 1 to 42 Days)

Among subjects in the *all vaccinated population*, there were 16 events of TTS—including venous thromboembolism (VTE), DVT, cerebral venous sinus thrombosis (CVST), and splanchnic thrombosis with thrombocytopaenia—identified in CPRD, 5 in SIDIAP, 2 in ARS Toscana, and none in PHARMO.

In the current study in CPRD, events of TTS occurred among subjects aged 20 to 69 years, and 9 of 16 (56.3%) were males. The crude IRs (95% CIs) per 10,000 person-years were similar across these age categories; the highest point estimate was 0.20 (< 0.01-30.47) for the age category 20 to 29 years, although CIs overlapped with estimates for other age categories. In the pre-pandemic ACCESS project in CPRD, there were no events of CVST with thrombocytopaenia, and the IR per 10,000 person-years of VTE with thrombocytopaenia was the highest among males aged 70 to 79 years (IR 0.014 in 2017 and 2018). There were no TTS

events among males aged 20 to 29 years, and the IR among females aged 20 to 29 years was 0.052 (in 2018). In the study by Burn et al [5], in CPRD Aurum, the median (Q1, Q3) age was 39 (22, 27) years, 50% were males, and the IR per 10,000 person-years was 0.15 for DVT with thrombocytopaenia, 0.01 for CVST with thrombocytopaenia, and 0.1 for pulmonary embolism with thrombocytopaenia [5].

In the current study in SIDIAP, events of TTS occurred among the subjects aged 40 to 69 years, and [redacted] were males. The highest IR (95% CI) per 10,000 person-years was 0.41 (0.00-61.11) among subjects aged 40 to 49 years. In the pre-pandemic ACCESS project in SIDIAP, CVST with thrombocytopaenia events were observed only among females aged 60 to 79 years, and the highest IR per 10,000 person-years was among females aged 70 to 79 years (0.15 in 2018). Also in the ACCESS project in SIDIAP, the IR of VTE with thrombocytopaenia was highest among males aged 70 to 79 years (IR 0.46 in 2020), followed by males aged 80+ years (0.29 in 2020). Among females, the highest IR was observed for the group aged 60 to 69 years (1.33 in 2020). In the study by Burn et al [5], in SIDIAP, the median (Q1, Q3) age was 42 (25, 59) years, 49.3% were males, and the IR per 10,000 person-years was 0.62 for DVT with thrombocytopaenia, 0.25 for superficial vein thrombosis with thrombocytopaenia, 0.59 for pulmonary embolism with thrombocytopaenia, and 0.01 for CVST with thrombocytopaenia [5].

In ARS Toscana, there was 1 event of TTS among subjects aged 50 to 59 years (IR 0.27 [0.00-70.64]) and 1 event of TTS among subjects aged 70 to 79 years (IR 0.06 [0.00-34.02]); both (100%) were females. In the ACCESS project, CVST with thrombocytopaenia events were observed only in males aged 70 to 79 years (IR 0.084) and in males aged 40 to 49 years (IR 0.063). The IR per 10,000 person-years of VTE with thrombocytopaenia was highest among males aged 60 to 69 years (IR 0.47 in 2017), followed by males aged 70 to 79 years (0.45 in 2017). The highest IR among females was observed in the group aged 80+ years (0.43 in 2019).

No major differences were found between the *all vaccinated population* and the AZD1222 matched cohort. In data sources with at least 1 event, the IRs (95% CI) per 10,000 person-years of TTS among the vaccinated AZD1222 matched cohorts ranged from 0.17 (0.09-0.28) in CPRD to 0.67 (0.22-1.56) in SIDIAP. Among subjects in the unvaccinated matched cohorts, [redacted] of TTS were identified in CPRD, 5 in SIDIAP, 7 in ARS Toscana, and none in PHARMO. In data sources with at least 1 event, the IR (95% CI) per 10,000 person-years ranged from 0.01 (0.01-0.04) in CPRD to 0.37 (0.10-1.35) in ARS Toscana. Overall, the combination of thrombocytopaenia with thrombosis was very infrequent in all data sources, and the IRs were low, leading to low precision of the estimates. The IRs of TTS tended to be higher among subjects in the AZD1222 cohorts than among subjects in the unvaccinated cohorts; except in PHARMO and in subjects in the unvaccinated cohort in

CPRD, most were higher than the standardised IR derived from the ACCESS project for VTE with thrombocytopaenia (see Figure 6).

Overall, in the studies evaluating background rates in the pre-pandemic period, distribution of events of TTS by age and sex showed that these were more frequent among older males. In this interim analysis, with very few events, TTS events were more frequent in younger age groups and were more frequent in males in CPRD and SIDIAP, although only females were identified with TTS in ARS Toscana. In PHARMO, free text was used to identify TTS, but no events were found. In addition, both free-text searches and ICPC codes were used to identify VTE and thrombocytopaenia but did not include CVST nor splanchnic thrombosis, thus further evaluation of the definition used in PHARMO will be performed in the next interim analysis. Similarly, the evaluation of TTS by location of the thrombosis and validation of TTS events will be performed in future analyses.

Thrombosis Without Thrombocytopaenia (Risk Window: 1 to 42 Days)

Among subjects in the AZD1222 matched cohorts, 22 events of thrombosis without thrombocytopaenia were identified in CPRD, while very few events were identified in the other data sources. In PHARMO, no events were identified. In data sources with at least 1 event, the IRs (95% CI) per 10,000 person-years ranged between 0.13 (0.00-0.75) in SIDIAP to 0.28 (0.03-1.02) in ARS Toscana. Among subjects in the unvaccinated matched cohorts, there were 27 events of thrombosis in CPRD, [redacted] in SIDIAP, 4 in ARS Toscana, and none in PHARMO. The IR (95% CI) per 10,000 person-years in the data sources with at least 1 event ranged from 0.08 (0.02-0.32) in SIDIAP to 0.21 (0.03-1.52) in ARS Toscana. Overall, thrombosis events without thrombocytopaenia were infrequent in all data sources, except in CPRD. Similarly, the IRs were low, leading to low precision of the estimates. These IRs were likely driven by the most frequent component, VTE, and were considerably lower than the standardised IR derived from ACCESS for VTE without thrombosis (see Figure 6) and were lower than the IRs for DVT reported by Burn et al [4] (pre-pandemic background rates) and by Pottegård et al [28] (AZD1222 vaccinees). This finding deserves further evaluation.

Thrombocytopaenia With Associated Bleeding (Risk Window: 1 to 42 Days)

Among subjects in the AZD1222 matched cohorts, only 6, 5, and 1 events were identified in CPRD, SIDIAP, and ARS Toscana, respectively. No events were identified in PHARMO. In data sources where at least 1 event was identified, the IR (95% CI) per 10,000 person-years among vaccinated subjects ranged from 0.07 (0.02-0.15) in CPRD to 0.67 (0.22-1.56) in SIDIAP. Among subjects in the unvaccinated matched cohorts, [redacted] identified in CPRD, 7 in SIDIAP, 10 in ARS Toscana, and none in PHARMO. The IR (95% CI) per 10,000 person-years in data sources with at least 1 event ranged from 0.01 (0.00-0.04) in CPRD to 0.53 (0.19-1.51) in ARS Toscana. Overall, the combination of thrombocytopaenia with bleeding occurred very infrequently in all data sources, and the IRs were low, leading to low precision of the estimates. In the study by Pottegård et al [28] (vaccination period),

several types of bleeding events were evaluated, with haematuria being the most frequent event among AZD1222 vaccinees. The combination of thrombocytopaenia with bleeding has not been evaluated in studies assessing background rates in the pre-pandemic period.

Thrombocytopaenia (Risk Window: 1 to 42 Days)

Among subjects in the AZD1222 matched cohorts, the IR (95% CI) per 10,000 person-years for thrombocytopaenia ranged from 1.56 (0.78-2.78) in ARS Toscana to 15.81 (13.08-18.93) in SIDIAP. Among subjects in the unvaccinated matched cohorts, the IR (95% CI) ranged from 1.74 (0.66-4.56) in PHARMO to 22.18 (18.52-26.55) in SIDIAP. Overall, the number of events was low in some data sources, and estimates differed by data source, especially in SIDIAP where IRs were higher. The IRs observed in CPRD and SIDIAP were higher than the standardised IRs derived from the ACCESS project, while the IRs in ARS Toscana and PHARMO were similar to the standardised IRs derived from the ACCESS project (see Figure 6).

In the current study, as in ACCESS, thrombocytopaenia was ascertained using diagnostic codes, and no evaluation of laboratory platelet levels was performed. In the study by Burn et al [5], the IR of coagulopathies was estimated separately by type, and thrombocytopaenia was ascertained using laboratory platelet levels in addition to diagnostic codes. In that study, coagulopathies were rare, and the highest IR (95% CI) per 10,000 person-years was observed for immune thrombocytopaenia that was 4.67 (4.57-4.77). In a study by Pottegård et al [28], in which outcomes were ascertained using data from inpatient stays and hospital outpatient clinic contacts among AZD1222 vaccinees, the IR per 10,000 person-years of thrombocytopaenia was 1.5 in Denmark and 3.8 in Norway.

Narcolepsy (Risk Window: 1 to 42 Days)

Among subjects in the AZD1222 matched cohorts, narcolepsy events were identified only in CPRD (23 events) and SIDIAP ([redacted]). The IR (95% CI) per 10,000 person-years observed was 0.26 (0.16-0.39) in CPRD and 0.27 (0.03-0.97) in SIDIAP. Among subjects in the unvaccinated matched cohorts, narcolepsy events were also identified only in CPRD and SIDIAP, and the IRs (95% CI) per 10,000 person-years were very similar to those observed among subjects in the AZD1222 matched cohorts, 0.28 (0.15-0.53) in CPRD and 0.29 (0.08-1.00) in SIDIAP. Overall, the number of events was low, and the CIs were wide. In both data sources, the IRs were higher than the standardised IRs derived from the ACCESS project (see Figure 6).

Acute Aseptic Arthritis (Risk Window: 1 to 42 Days)

As discussed in Section 9.4.2, no specific codes (“narrow” definition) were identified to define of acute aseptic arthritis. Therefore, a broader definition with only “possible” codes such as gout, arthritis, chondrocalcinosis, and crystal arthropathies was used to identify these events. In PHARMO, free-text searches for a narrower definition was applied, although the

more general ICPC code for arthritis was also used as in the other data sources. Among subjects in the AZD1222 matched cohorts, the IR (95% CI) per 10,000 person-years ranged from 2.42 (0.79-5.65) in PHARMO to 87.20 (85.26-89.18) in CPRD. Among subjects in the unvaccinated matched cohorts, the IR (95% CI) per 10,000 person-years ranged from 3.61 (1.74-7.48) in PHARMO to 42.24 (41.36-43.13) in CPRD. Overall, estimates differed by data source and by cohort. In the ACCESS project, acute aseptic arthritis was evaluated only in CPRD, and the derived standardised IR was lower than the IRs estimated in this interim analysis) (see Figure 6). Further evaluation of the codes used in each study and data source is planned.

Guillain-Barré Syndrome (Risk Window: 1 to 42 Days)

Among subjects in the AZD1222 matched cohort, no events were identified in PHARMO. In the data sources with at least 1 event identified, the IR (95% CI) per 10,000 person-years for Guillain-Barré syndrome ranged from 0.28 (0.03-1.02) in ARS Toscana to 1.20 (0.55-2.29) in SIDIAP. Among subjects in the unvaccinated matched cohorts, the IR (95% CI) per 10,000 person-years ranged from 0.23 (0.12-0.42) in CPRD to 0.79 (0.28-2.24) in SIDIAP. Overall, the precision of the estimates was low in some data sources, except in CPRD. The IRs varied between cohorts and across data sources. Estimates in SIDIAP where higher than the standardised IRs derived from the ACCESS project, while the risk estimates for CPRD, ARS Toscana, and PHARMO were similar to those observed in the ACCESS project (see Figure 6).

Postural Orthostatic Tachycardia Syndrome (Risk Window: 1 to 42 Days)

Postural orthostatic tachycardia syndrome was captured only in CPRD because no ICD or ICPC codes were available for this diagnosis. The IR (95% CI) per 10,000 person-years observed was 0.62 (0.47-0.80) per 10,000 person-years among subjects in the AZD1222 matched cohort and 0.37 (0.25-0.54) among subjects in the unvaccinated matched cohort. This AESI has not been evaluated in studies assessing background rates in the pre-pandemic period.

Acute Cardiac Injury Including Microangiopathy, Cardiogenic Shock, Heart Failure (Risk Window: 1 to 90 Days)

Among subjects in the AZD1222 matched cohorts, the IR (95% CI) per 10,000 person-years ranged from 21.05 (16.28-26.78) in PHARMO to 41.10 (40.15-42.07) in CPRD. Among subjects in the unvaccinated matched cohorts, the IR (95% CI) per 10,000 person-years ranged from 17.43 (12.04-25.23) in PHARMO to 61.71 (56.83-67.01) in ARS Toscana. Because this composite AESI has not been evaluated in the ACCESS project, a visual comparison of the IRs of heart failure, the most common component of this AESI, has been performed in Figure 6. Compared with the standardised IR for heart failure derived from the ACCESS project, in CPRD and SIDIAP, the IRs for acute cardiac injury were higher, while the IRs in PHARMO and among subjects in the unvaccinated cohort in ARS Toscana were similar, and the IRs among subjects in the AZD1222 cohort in ARS Toscana were lower (see Figure 6).

Stress Cardiomyopathy (Risk Window: 1 to 42 Days)

Among subjects in the AZD1222 matched cohorts, the IR (95% CI) per 10,000 person-years ranged from 0.49 (0.36-0.66) in CPRD to 0.80 (0.29-1.75) in SIDIAP, and no events were identified in PHARMO. Among subjects in the unvaccinated matched cohorts, IRs (95% CI) per 10,000 person-years ranged from 0.13 (0.02-0.95) in PHARMO to 0.80 (0.43-1.50) in ARS Toscana. Overall, stress myocardiopathy was an infrequent event in all data sources, and the precision of the estimates was low. Compared with the standardised IR derived from the ACCESS project, the IR was higher in SIDIAP and lower in ARS Toscana; no estimates were produced for CPRD and PHARMO (see Figure 6).

Myocardial Infarction (Risk Window: 1 to 28 Days)

Among subjects in the AZD1222 matched cohorts, the IR (95% CI) per 10,000 person-years ranged from 4.12 (1.51-8.97) in PHARMO to 22.51 (18.49-27.16) in ARS Toscana. Among subjects in the unvaccinated matched cohorts, the IR (95% CI) per 10,000 person-years ranged from 9.36 (2.54-34.46) in PHARMO to 30.45 (26.58-34.88) in ARS Toscana. Overall, the IRs were similar between data sources, except in PHARMO, where IRs were lower. The background IR of myocardial infarction was not evaluated in the ACCESS project. In the study by Li et al [23], the IR per 10,000 person-years for acute myocardial infarction, reported in SIDIAP by age and sex, was 64.64 among males aged 65 to 74 years and 20.48 among females aged 65 to 74 years.

Myocarditis/Pericarditis (Risk Window: 1 to 42 Days)

Among subjects in the AZD1222 matched cohorts, 180 events were identified in CPRD, 18 in SIDIAP, 47 in ARS Toscana, and none in PHARMO. In the data sources with at least 1 event, the IR (95% CI) per 10,000 person-years ranged from 2.02 (1.74-2.34) in CPRD to 6.65 (4.89-8.85) in ARS Toscana. Among subjects in the unvaccinated matched cohorts, 355 events were identified in CPRD, 73 in SIDIAP, 337 in ARS Toscana, and [redacted] in PHARMO. The IR (95% CI) per 10,000 person-years ranged from 0.13 (0.02-0.95) in PHARMO to 18.06 (15.18-21.48) in ARS Toscana. Overall, myocarditis and pericarditis were very infrequent in PHARMO and more frequent in ARS Toscana, which was in line with what was observed in the ACCESS project. Also, the IRs were similar to the standardised IRs derived from the ACCESS project, except in ARS Toscana, where they were higher than those observed in ACCESS (see Figure 6).

Acute Kidney Injury (Risk Window: 1 to 14 Days)

Among subjects in the AZD1222 matched cohorts, the IR (95% CI) per 10,000 person-years ranged from 9.34 (5.92-14.01) in ARS Toscana to 46.06 (32.08-64.06) in PHARMO. Among subjects in the unvaccinated matched cohorts, the IR (95% CI) per 10,000 person-years ranged from 29.98 (27.66-32.50) in CPRD to 37.47 (32.06-43.80) in SIDIAP. Overall, there were differences in the IRs estimated between cohorts and between data sources. Compared with

the standardised IRs derived from the ACCESS project, the IRs observed in interim analysis 1 were lower in SIDIAP and in ARS Toscana among subjects in the AZD1222 cohorts, but higher in CPRD and PHARMO and among subjects in the unvaccinated cohort in ARS Toscana (see Figure 6).

Acute Liver Injury (Risk Window: 1 to 14 Days)

Among subjects in the AZD1222 matched cohort, no acute liver injury events were identified in PHARMO. Among the data sources with at least 1 event identified, the IR (95% CI) per 10,000 person-years ranged from 1.62 (0.44-4.16) in ARS Toscana to 2.43 (0.98-5.00) in SIDIAP. Among subjects in the unvaccinated matched cohorts, the IRs (95% CI) per 10,000 person-years ranged from 0.32 (0.05-2.30) in PHARMO, where only [redacted] identified, to 10.17 (7.61-13.58) in SIDIAP. The IR of acute liver injury among subjects in the unvaccinated cohort in SIDIAP was higher than the IR observed in any other cohort and data source. Overall, acute liver injury was an infrequent event, and it is possible that was poorly ascertained in PHARMO. The IRs in were lower than the standardised IRs derived from the ACCESS project, except in CPRD where IRs were higher (see Figure 6).

Transverse Myelitis (Risk Window: 1 to 90 Days)

Among subjects in the AZD1222 matched cohorts, no transverse myelitis events were identified in SIDIAP nor in PHARMO. In CPRD and in ARS Toscana, the IR (95% CI) per 10,000 person-years was 0.27 (0.20-0.36) and 0.16 (0.02-0.56), respectively. Among subjects in the unvaccinated matched cohorts, no events were identified in PHARMO, and only [redacted] identified in SIDIAP. The IR (95% CI) per 10,000 person-years ranged from 0.03 (0.00-0.19) in SIDIAP to 0.18 (0.10-0.32) in CPRD. Overall, transverse myelitis was a very infrequent event among subjects in both cohorts, and the precision of the CIs was low. The IRs of transverse myelitis in interim analysis 1 were similar to the standardised IRs derived from the ACCESS project, except in CPRD, where they were higher (see Figure 6).

Encephalitis (Including Acute Disseminated Encephalomyelitis) (Risk Window: 1 to 42 Days)

Among subjects in the AZD1222 matched cohorts, the IRs (95% CI) per 10,000 person-years ranged from 0.47 (0.34-0.64) in CPRD to 1.94 (0.53-4.96) in PHARMO. Among subjects in the unvaccinated matched cohorts, the IR (95% CI) per 10,000 person-years ranged from 0.13 (0.02-0.95) in PHARMO to 0.75 (0.38-1.49) in ARS Toscana. Overall, the IRs among vaccinated and unvaccinated subjects and across data sources were similar and also similar to the standardised IRs derived from the ACCESS project, except for those among subjects in the AZD1222 cohort in PHARMO, which were higher (see Figure 6).

Other Peripheral and Polyneuropathies (Risk Window: 1 to 42 Days)

Among subjects in the AZD1222 matched cohorts, the IR (95% CI) per 10,000 person-years ranged from 1.27 (0.58-2.42) in ARS Toscana to 10.45 (8.26-13.04) in SIDIAP. In PHARMO,

this AESI could not be ascertained. Among subjects in the unvaccinated matched cohorts, the IR (95% CI) per 10,000 person-years ranged from 2.30 (1.39-3.80) in ARS Toscana to 11.60 (9.35-14.39) in SIDIAP. Overall, estimates differed by data source, although they were similar between cohorts. This AESI has not been evaluated in studies assessing background rates in the pre-pandemic period.

Generalised Convulsions (Risk Window: 0 to 14 Days)

Among subjects in the AZD1222 matched cohorts, the IR (95% CI) per 10,000 person-years ranged from 1.22 (0.03-6.78) in PHARMO to 15.55 (14.21-16.98) in CPRD. Among subjects in the unvaccinated matched cohorts, the IR (95% CI) per 10,000 person-years ranged from 0.89 (0.29-2.77) in PHARMO to 15.97 (12.66-20.15) in ARS Toscana. The IRs differed by cohort and by data source; compared with the standardised IRs derived from the ACCESS project, IRs were higher in CPRD and SIDIAP, but lower in PHARMO and in subjects in the AZD1222 matched cohort in ARS Toscana (see Figure 6).

Optic Neuritis/Neuromyelitis Optica Spectrum Disorder (Risk Window: 1 to 42 Days)

This AESI was not captured in PHARMO. Among subjects in the AZD1222 matched cohorts, few events of optic neuritis/neuromyelitis optica spectrum disorder were captured in the data sources, with IRs (95% CI) per 10,000 person-years ranging from 0.28 (0.03-1.02) in ARS Toscana to 1.20 (0.55-2.29) in SIDIAP. Among subjects in the unvaccinated matched cohorts, the IR (95% CI) per 10,000 person-years ranged from 0.32 (0.13-0.81) in ARS Toscana to 0.75 (0.32-1.80) in SIDIAP. Overall, the number of events was low in most data sources, leading to low precision of the estimates in those data sources. This AESI has not been evaluated in studies assessing background rates in the pre-pandemic period.

Bell's Palsy (Risk Window: 1 to 42 Days)

Among subjects in the AZD1222 matched cohorts, the IR (95% CI) per 10,000 person-years was higher in PHARMO and SIDIAP, 16.48 (11.41-23.03) and 9.91 (7.78-12.44), respectively, than in CPRD and ARS Toscana, 5.44 (4.97-5.95) and 2.55 (1.51-4.02), respectively. Among subjects in the unvaccinated matched cohorts, PHARMO and SIDIAP had higher IRs (95% CI) per 10,000 person-years, 17.66 (12.02-25.94) and 11.92 (9.41-15.09), respectively, than CPRD and ARS Toscana with 3.69 (3.18-4.28) and 3.00 (2.04-4.41), respectively. The background rate of this AESI in the pre-pandemic period was not evaluated in the ACCESS project, but was assessed by Li et al [23] in CPRD GOLD, SIDIAP (primary care data linked to hospital data), and in a primary care data source in the Netherlands. The IRs observed in PHARMO were higher than the IRs observed in Li et al [23], while the IR observed in CPRD were similar than the IRs observed in Li et al. Finally, IRs in SIDIAP were lower than the IRs obtained in SIDIAP by Li et al [23].

Anaphylaxis (Risk Window: 0 to 14 Days)

Among subjects in the AZD1222 matched cohorts, few events occurred in all data sources except in PHARMO. The PP (95% CI) per 10,000 subjects ranged from 0.06 (0.01-0.21) in ARS Toscana to 2.34 (1.67-3.20) in PHARMO. Similarly, among subjects in the unvaccinated matched cohorts, PP (95% CI) per 10,000 subjects ranged from 0.03 (0.01-0.05) in SIDIAP to 1.06 (0.84-1.30) in PHARMO. Prevalence proportions in CPRD, SIDIAP, and ARS Toscana were lower than the standardised IR derived from ACCESS except for PHARMO, for which the PPs were higher than the standardised IR derived from the ACCESS project. The outcome was also evaluated by Li et al [23]. The PPs observed in vaccinated subjects in CPRD and SIDIAP were lower than the crude IRs observed in the study by Li et al [23], while the PP observed in PHARMO in vaccinated subjects was similar to the IR obtained in the primary care data source in the Netherlands by Li et al [23].

Rhabdomyolysis (Risk Window: 1 to 42 Days)

Among subjects in the AZD1222 matched cohorts, few events of rhabdomyolysis were captured in all data sources, with IRs (95% CI) per 10,000 person-years ranging from 0.42 (0.09-1.24) in ARS Toscana to 0.97 (0.12-3.50) in PHARMO. Among subjects in the unvaccinated matched cohorts, IRs (95% CI) per 10,000 person-years ranged from 0.83 (0.60-1.16) in CPRD to 1.98 (1.14-3.42) in ARS Toscana. This AESI has not been evaluated in studies assessing background rates in the pre-pandemic period.

Multisystem Inflammatory Syndrome in Adults/Children (Risk Window: 1 to 42 Days)

Among subjects in the AZD1222 matched cohorts, only [redacted] were identified in SIDIAP and no events were identified in the other data sources. The IR (95% CI) per 10,000 person-years in SIDIAP was 0.27 (0.03-0.97). Among subjects in the unvaccinated matched cohorts, [redacted] were identified in SIDIAP, and no events were identified in the other data sources. The IR (95% CI) per 10,000 person-years in SIDIAP was 0.08 (0.02-0.32). Compared with standardised IRs derived from the ACCESS project, the IRs observed in CPRD and PHARMO were similar, while the IRs observed in SIDIAP were higher (see Figure 6).

Sudden Death (Risk Window: 0 to 6 Days)

Among subjects in the AZD1222 matched cohorts, [redacted] were identified in PHARMO, with a PP (95% CI) per 10,000 subjects of 0.18 (0.04-0.52), and [redacted] identified in CPRD, with a PP (95% CI) per 10,000 subjects of 0.00 (0.00-0.01). No events were identified in SIDIAP nor ARS Toscana. Among subjects in the unvaccinated matched cohorts, 48 events were found in PHARMO, [redacted] in CPRD, and 1 event in ARS Toscana. The PP (95% CI) per 10,000 subjects ranged from 0.01 (0.00-0.03) in ARS Toscana to 0.59 (0.43-0.78) in PHARMO. No events were found in SIDIAP. Compared with standardised IRs derived from the ACCESS project, the PPs observed in vaccinated subjects in CPRD and ARS Toscana

were similar, while the IRs observed in SIDIAP were lower. No IRs were provided from PHARMO for this specific AESI in the ACCESS project (see Figure 6).

Acute Respiratory Distress Syndrome (ARDS) (Risk Window: 1 to 28 Days)

Among subjects in the AZD1222 matched cohorts, the highest IR (95% CI) per 10,000 person-years was observed in SIDIAP with 4.12 (2.58-6.24), followed by PHARMO with 1.37 (0.17-4.96), ARS Toscana with 1.24 (0.45-2.69), and CPRD with 0.89 (0.67-1.17). Among subjects in the unvaccinated matched cohorts, the IRs (95% CI) per 10,000 person-years were higher in SIDIAP and ARS Toscana, 10.41 (7.97-13.59) and 7.57 (5.60-10.24), respectively, compared with CPRD and PHARMO, 1.22 (0.88-1.69) and 0.18 (0.03-1.28), respectively. The IRs observed in CPRD, PHARMO, and among subjects in the AZD1222 cohort in ARS Toscana were lower than standardised IRs derived from the ACCESS project. The IRs observed in SIDIAP were higher than the standardised IRs derived from the ACCESS project (see Figure 6).

11.1.2 AESIs With Unknown Risk Windows (Risk Window Ending at 180 or 365 Days)

Myasthenia Gravis (Risk Window: 1 to 365 Days)

Among subjects in the AZD1222 matched cohorts, the cumulative incidence (95% CI) per 10,000 subjects was low, with estimates ranging from 0.12 (0.00-22.44) in ARS Toscana to 0.69 (0.00-6.73) in CPRD. Among subjects in the unvaccinated matched cohorts, the cumulative incidence (95% CI) per 10,000 subjects ranged from 0.14 (0.00-10.12) in ARS Toscana to 0.17 (0.00-2.89) in CPRD. Myasthenia gravis could not be evaluated in PHARMO due to lack of specific ICPC codes and the available free-text searches. This AESI has not been evaluated in studies assessing background rates in the pre-pandemic period.

Autoimmune Thyroiditis (Risk Window: 1 to 180 Days)

Among subjects in the AZD1222 matched cohorts, the highest cumulative incidence was observed in ARS Toscana with 6.69 (95% CI, 0.00-28.87) events per 10,000 subjects. CPRD and SIDIAP had similar cumulative incidences (95% CI) per 10,000 subjects, 2.53 (0.00-8.58) and 2.15 (0.00-16.35), respectively, while in PHARMO, the cumulative incidence (95% CI) was 0.08 (0.01-27.98). Among subjects in the unvaccinated matched cohorts, cumulative incidence (95% CI) per 10,000 subjects ranged from 2.09 (0.00-8.27) in SIDIAP to 8.71 (0.00-18-75) in ARS Toscana. No events were found in PHARMO. This AESI has not been evaluated in studies assessing background rates in the pre-pandemic period.

Capillary Leak Syndrome (Risk Window: 1 to 365 Days)

Among subjects in the AZD1222 matched cohorts, only [redacted] of capillary leak syndrome [redacted] captured in CPRD, with a cumulative incidence (95% CI) per 10,000 subjects of 0.00 (0.00-6.05). In the other data sources, this AESI could not be evaluated due to the absence of

"narrow" codes in ICD or ICPC coding systems. Among subjects in the unvaccinated matched cohort, no events were captured in CPRD. This AESI has not been evaluated in studies assessing background rates in the pre-pandemic period.

Acute Pancreatitis (Risk Window: 1 to 365 Days)

Among subjects in the AZD1222 matched cohorts, the highest cumulative incidence (95% CI) per 10,000 subjects was observed in CPRD with 5.15 (0.00-11.21), followed by ARS Toscana with 2.86 (0.00-25.19), and SIDIAP with 1.80 (0.00-16.00). Only [redacted] captured in PHARMO. Among subjects in the unvaccinated matched cohorts, the highest cumulative incidence (95% CI) per 10,000 subjects was also observed in CPRD with 3.35 (0.60-6.10) and the lowest in PHARMO with 0.10 (0.00-11.51). This AESI has not been evaluated in studies assessing background rates in the pre-pandemic period.

Multiple Sclerosis and Other Demyelinating Disorders (Risk Window: 1 to 365 Days)

Among subjects in the AZD1222 matched cohorts, the cumulative incidence (95% CI) per 10,000 subjects ranged from 0.48 (0.00-28.38) in PHARMO to 3.83 (0.00-9.88) in CPRD. Among subjects in the unvaccinated matched cohorts, the cumulative incidence (95% CI) per 10,000 subjects ranged from 0.15 (0.00-11.56) in PHARMO to 2.73 (0.00-5.53) in CPRD. This AESI has not been evaluated in studies assessing background rates in the pre-pandemic period.

Fibromyalgia (Risk Window: 91 to 365 Days)

Among subjects in the AZD1222 matched cohorts, similar cumulative incidences (95% CI) per 10,000 subjects were observed in CPRD and SIDIAP, 8.74 (1.11-16.38) and 8.91 (0.00-40.86), respectively. However, 36% and 83% of AZD1222 subjects, respectively, were censored prior to the start of the risk window at 91 days after index date. Fibromyalgia could not be assessed in ARS Toscana and PHARMO. Among subjects in the unvaccinated matched cohorts, the cumulative incidence (95% CI) per 10,000 subjects was higher in SIDIAP with 8.92 (0.00-24.71) than in CPRD with 5.06 (0.00-10.40). This AESI has not been evaluated in studies assessing background rates in the pre-pandemic period.

Chronic Fatigue Syndrome/ME/PVFS (Risk Window: 183 to 365 Days)

Among subjects in the AZD1222 matched cohort, 5 events were captured in CPRD with a cumulative incidence (95% CI) per 10,000 subjects of 0.56 (0.00-22.74). No events were found in ARS Toscana. This AESI could not be assessed in SIDIAP and PHARMO. Among subjects in the unvaccinated matched cohort, only [redacted] found in CPRD, with a cumulative incidence (95% CI) per 10,000 subjects of 0.70 (0.00-18.30). No events were found in ARS Toscana. This AESI has not been evaluated in studies assessing background rates in the pre-pandemic period.

Anosmia/Ageusia (Risk Window: 1 to 365 Days)

Among subjects in the AZD1222 matched cohorts, the cumulative incidence (95% CI) per 10,000 subjects ranged from 1.18 (0.00-29.09) in PHARMO to 7.81 (1.74-13.88) in CPRD. No events were found in ARS Toscana. Among subjects in the unvaccinated matched cohorts, the cumulative incidence (95% CI) per 10,000 subjects ranged from 1.59 (0.00-13.02) in PHARMO to 9.60 (3.48-15.72) in CPRD. No events were found in ARS Toscana. The cumulative incidences observed in CPRD and in PHARMO were higher than standardised IRs derived from the ACCESS project, while the cumulative incidences observed in SIDIAP and ARS Toscana were similar to the standardised IRs derived from the ACCESS project (see Figure 7).

Type III Hypersensitivity Reactions (Risk Window: 1 to 365 Days)

Among subjects in the AZD1222 matched cohorts, the cumulative incidence (95% CI) per 10,000 subjects ranged from 2.57 (0.00-24.90) in ARS Toscana to 19.71 (13.29-26.13) in CPRD. Among subjects in the unvaccinated matched cohorts, the cumulative incidence (95% CI) per 10,000 subjects ranged from 3.31 (0.00-9.50) in SIDIAP to 7.75 (5.01-10.49) in CPRD. This AESI could not be assessed in PHARMO. This AESI has not been evaluated in studies assessing background rates in the pre-pandemic period.

Vaccine-Associated Enhanced Disease, Including Vaccine-Associated Enhanced Respiratory Disease, Including ARDS (Risk Window: 14 to 365 Days)

Among subjects in the AZD1222 matched cohorts, few events of vaccine-associated enhanced disease were captured in all data sources, with low cumulative incidences. Specifically, the cumulative incidence (95% CI) per 10,000 subjects ranged from 0.19 (0.00-34.08) in PHARMO to 0.71 (0.00-19.01) in SIDIAP. No events were captured in CPRD. Among subjects in the unvaccinated matched cohorts, cumulative incidence (95% CI) per 10,000 subjects ranged from 0.04 (0.00-16.57) in PHARMO to 2.15 (0.00-11.34) in ARS Toscana. This AESI has not been evaluated in studies assessing background rates in the pre-pandemic period.

Erythema Multiforme (Risk Window: 1 to 365 Days)

Among subjects in the AZD1222 matched cohorts, the cumulative incidence (95% CI) per 10,000 subjects was low for all data sources, ranging from 0.06 (0.00-27.96) in PHARMO to 0.43 (0.00-22.75) in ARS Toscana. Among subjects in the unvaccinated matched cohorts, similar cumulative incidences (95% CI) per 10,000 subjects ranged from 0.20 (0.00-2.92) in CPRD to 0.26 (0.00-10.24) in ARS Toscana. No events were found in PHARMO for unvaccinated subjects. The cumulative incidences observed in CPRD, SIDIAP, ARS Toscana, and PHARMO were similar to standardised IRs derived from the ACCESS project (see Figure 7).

Chilblain-Like Skin Lesions (Risk Window: 1 to 365 Days)

Among subjects in the AZD1222 matched cohorts, the cumulative incidence (95% CI) per 10,000 subjects ranged from 0.03 (0.00-22.35) in ARS Toscana to 1.01 (0.00-7.05) in CPRD. Among subjects in the unvaccinated matched cohorts, cumulative incidence (95% CI) per 10,000 subjects ranged from 0.37 (0.00-11.79) in PHARMO to 0.59 (0.00-6.76) in SIDIAP. No events were found in ARS Toscana. The cumulative incidences observed in CPRD, SIDIAP, ARS Toscana, and PHARMO were similar to standardised IRs derived from the ACCESS project (see Figure 7).

11.2 Limitations

The results of interim analysis 1 must be evaluated in view of the study limitations.

Selection bias: Over the course of the study, the population of potential comparators who remain unvaccinated may be systematically different from those who choose to be vaccinated. The age restrictions on the use of AZD1222 imposed in the UK, Spain, Italy, and the Netherlands made it difficult to find comparable controls for the cohort study. However, results of the current interim analysis 1 showed that subjects vaccinated with AZD1222 could be matched to concurrent unvaccinated controls in a ratio of 1:5 that was achieved in all data sources. An SCRI analysis, which includes only vaccinated individuals, will be conducted in the final analysis to evaluate the risk of AESIs for outcomes that are suitable for this design.

Confounding: Although vaccinated and unvaccinated subjects were matched on calendar date, age, sex, geographic region, and history of COVID-19 infection, the decision to remain unvaccinated may also be related to lifestyle choices that are difficult to measure. The final analysis will include an SCRI design to address potential confounding. The SCRI design adjusts for time-invariant confounders, and using only postvaccination control periods will avoid the potential bias that use of prevaccination control periods may introduce, as prevaccination health events may affect the probability of exposure. However, the SCRI design is not well suited to study outcomes with gradual onset, long latency, or risk periods that are not well known.

Informative censoring: There are differences between AZD1222-vaccinated subjects and concurrent unvaccinated comparators in the proportion of subjects censored due to informative reasons (ie, subjects are lost to follow-up due to reasons related to the study [16; 18]). However, the decision on adjustment of future comparative analysis for potential informative censoring will be made at the time of analyses for interim report 2, when the study period is expected to have at least 1 year of follow-up in all or almost all data sources. This will allow observation of the final distribution of the proportions of subjects censored for the different reasons for censoring. It is expected that the proportion of AZD1222-vaccinated subjects censored due to receiving boosters will increase when a longer study period is included.

Exposure misclassification: Exposure identification was based on pharmacy dispensing records, general practice records, immunisation registers, medical records, and other secondary data sources. The ability to identify specific COVID-19 vaccine products and dates of vaccination in the participating data sources is considered complete with the exception of PHARMO (see Section 9.4.1). The SCRI design, which includes only individuals who are known to be vaccinated, will also address remaining concerns in this area.

Outcome misclassification:

- For this interim report 1, the data extraction was performed during Q1 2022. Due to the lag time in the data sources (see Section 9.2, Table 4), for most of the AESIs with unknown risk windows (defined for the study as risk windows ending 180 or 365 days after the index date; see Table 5), these risk windows were not fully covered. Therefore, the probability of underestimation of risk estimates remains. In future analyses (ie, for interim reports 2 and 3 and the final analysis), at least 1 year of follow-up will be included; therefore, this risk will be minimised. This is particularly important for subjects vaccinated with AZD1222 since follow-up for 95% or more of these subjects were censored due to the end of study period. For concurrent unvaccinated subjects, a smaller percentage (19%-46%) were censored due to the end of study period. Implications of these results are discussed in the Interpretation, Section 11.3.2.
- Outcome misclassification cannot be discarded due to the type of data—eg, either GP data or hospital data, or both—and coding systems used in different data sources. In data sources where only GP data has been used, such as CPRD and PHARMO, it is possible that outcomes that usually require hospitalisation may have been misclassified, although GPs frequently include this information in the subjects' record. AESIs that are managed mainly by GPs are expected to be underrecorded in data sources that rely on inpatient data such as ARS Toscana. In addition, it is also expected that some AESIs such as anosmia or ageusia may have not required any contact with the healthcare system and thus may be underrecorded. Outcome misclassification may also occur due to scarce granularity of some coding systems such as the ICPC coding system used in GP data in the Netherlands or the ICD-9 coding system. Coding systems such as SNOMED used by CPRD are known to have a high level of granularity, while the opposite is true for ICPC used in PHARMO. Similarly, ICD-10 is known to have more granularity than ICD-9, which is used in ARS Toscana. These differences in granularity were so extreme that some AESIs could not be ascertained in some data sources. For example, 2 AESIs, postural orthostatic tachycardia and capillary leak syndrome, could be identified only through SNOMED codes, which are only available in CPRD. However, outcomes misclassification due to type of data and coding systems is not expected to be differential between vaccinated and unvaccinated subjects within the same data source. These differences in the type and availability of data and coding systems between data sources may explain the differences observed between data sources in the IRs for certain AESIs. This is in line with the

differences also observed in the ACCESS project, which evaluated pre-pandemic background rates [38].

- The coding lists for some AESIs were based on code lists used in ACCESS as a starting point and were latter reviewed by members of VAC4EU, including principal investigators of several studies, and by members of all data sources participating in the VAC4EU network. The research team plans to continue the review and refinements of these lists, focusing on harmonisation between coding systems and between related AESIs, and from knowledge developed within VAC4EU and the research community evaluating these AESIs in different observational studies.

Technical limitations: Limitations in computational capacity to undertake analysis with such a high number of subjects, essentially the whole data source population, the advanced methods planned for future analyses have been identified as an area of improvement for future analyses.

11.3 Interpretation

11.3.1 Vaccination Coverage and Distribution of Matching Variables

Vaccination coverage data were consistent with the national/regional data in ARS Toscana, SIDIAP, and CPRD [8; 24]. In PHARMO, as described in Section 9.4.1.5, because the GP Database used for interim report 1 does not contain all the vaccination records, and due to the process of data cleaning, the number of subjects vaccinated with AZD1222 was underrecorded. A decrease in the use of AZD1222 after Q2 2021 was expected given the restrictions applied as a result of the identification of thromboembolic events associated with adenovirus vaccines.

Age distribution was different between the UK and EU countries and in line with the vaccination strategies described by the European Centre for Disease Prevention and Control (ECDC) [8; 24] and the roll-out strategies applied by country/region (see Table 2 in Section 6). While in most of the EU countries AZD1222 was rolled out initially to the groups aged 60 years and older, use of AZD1222 was extensive and across all age groups in the UK, and this pattern was observed in the results for interim report 1. A lower proportion of subjects vaccinated with AZD1222 in the older age groups is in line with the EU vaccination strategies where vaccination was initially prioritised with Pfizer-BioNTech COVID-19 vaccine (Comirnaty) and targeted to elderly subjects, residents in long-term facilities, healthcare workers, and immunocompromised subjects. Vaccination of children with AZD1222 is unexpected; however, results from this interim analysis showed that it occurred rarely (< 0.01%) and may represent vaccination of immunocompromised children, although errors in data recording cannot be discarded.

Sex distribution is in line with population composition by age groups, ie, more females in the older age groups and the majority of the subjects vaccinated with AZD1222 were in the older age groups, leading to an overall higher proportion of females than males vaccinated with AZD1222.

Prior history of COVID-19 differed by data source from 3.21% in ARS Toscana, where information was based on either hospital diagnosis or positive PCR tests, to 12.37% in PHARMO, where a broader definition, which included free-text searches, was used. In SIDIAP and CPRD, ascertainment of prior COVID-19 was based on diagnosis, positive PCR tests, and also on positive antigen tests. Underrecording of COVID-19 is expected to differ by data source and country, and also during the whole study period within each country, driven by test availability and variation of testing and contact tracing policies over time. At the beginning of the COVID-19 pandemic, only PCR tests were available, but often only for the most severely affected patients. Later, and more frequently during late 2021 and 2022, many cases were confirmed through antigen testing and were frequently not reported, especially if mild or asymptomatic COVID-19, a situation that is expected to increase in 2022 as testing and tracking polices are withdrawn. This will likely lead to a larger misclassification of prior history of COVID-19 among subjects that received AZD1222 in late 2021 or later. It is expected that not many more subjects than those reported in interim report 1 will have received a first dose of AZD1222 in 2021. Note that the study period for interim report 1 in the UK CPRD already includes data through 13 of October 2021.

For interim analysis 1, only look-back data in the 12 months prior to the index date was used to define prior history of the AESIs of interest. For future analysis, the whole duration of the look-back period will be used to define most baseline comorbidities. The median duration of the look-back period was over 10 years for all data sources and is considered appropriate to ascertain prior history of diseases. In ARS Toscana, the look-back period was longer than in other data sources; quality of recording improved since 2009 and only these data will be used in future analyses.

11.3.2 Availability of Concurrent Unvaccinated Comparators and Duration of Follow-up in Matched Cohorts and Alternative Approaches

A 1:5 matching ratio of AZD1222 and unvaccinated was achieved in all data sources. However, the duration of follow-up among concurrent unvaccinated comparators (median duration range 1.1 to 1.4 months) was lower than in the AZD1222 group (median duration range 2.3 to 7.1 months). The follow-up accrued in both the vaccinated and in the unvaccinated groups covers the risk window required for the evaluation of AESIs with known risk windows. For the evaluation of AESIs with unknown risk windows (ie, those with a risk window that ends at 180 or 365 days), the results in the data sources with the longest study period (ARS Toscana, UK CPRD) indicate that the follow-up accrued among concurrent unvaccinated subjects was insufficient. In all data sources, in 51% to 79% of the unvaccinated

subjects, follow-up was censored due to having received any COVID-19 vaccine. A small percentage of unvaccinated subjects (19%-46%) were censored due to the end of study period. Therefore, mean duration of follow-up for these subjects will likely not be much longer when the end of the study period is extended for the next reports.

Among subjects vaccinated with AZD1222, 95% (ARS Toscana), 96% (CPRD, see footnote in Table 10) and 98% (SIDIAP and PHARMO) had their follow-up censored due to the end of study period for interim report 1; thus, it is possible that they will have longer durations of follow-up that may allow for the evaluation of AESIs with unknown risk windows for subsequent analyses. Based on the vaccination policies in the UK and the EU for subjects vaccinated with AZD1222, it is expected that receiving boosters of other COVID-19 vaccines will likely be the main reason for AZD1222 cohorts to have a follow-up of less than 1 year in future interim reports. This may affect the evaluation of AESIs with unknown risk windows in the AZD1222 cohorts.

In conclusion, for the reasons stated previously, the use of concurrent unvaccinated comparators is considered acceptable for the evaluation of AESIs with known risk windows and problematic for the evaluation of AESIs with unknown risk windows (those with risk windows ending at 180 or 365 days). Therefore, during the analyses for interim report 2, the marketing authorisation holder proposes evaluating the feasibility of using concurrent vaccinated comparators, based on information that does not require a protocol amendment, to estimate the number of subjects vaccinated with an mRNA vaccine (Pfizer or Moderna) and to describe their characteristics, focusing on key matching variables in the AZD1222 PASS: age, sex, and calendar time.

The approach of selecting active comparators is not without challenges due to the specific and time-varying vaccination policies in each country and even within regions. Concerns about using active comparators include study size, as well as confounding and selection bias.

- Regarding **study size**, assuming a matching ratio of 1:1, a 20% loss of vaccinated subjects due to lack of matches, and 4 million subjects vaccinated with AZD1222, the study would still have a 79% probability that the upper bound of the 95% CI would be below 2.5. However, a UK study [27] showed that for the most frequent age categories of AZD1222 vaccinees, more than twice times as many subjects were vaccinated with AZD1222 as with the Pfizer-BioNTech COVID-19 vaccine. For example, for the age categories of 40 to 49, 50 to 59, and 60 to 69 years, there were 4.4 million, 5.6 million, and 4 million subjects, respectively, vaccinated with AZD1222 and 1.4 million, 1.5 million, and 1.7 million subjects, respectively, vaccinated with the Pfizer-BioNTech COVID-19 vaccine. Given its less directive and restrictive vaccination policies, the UK is likely a best-case scenario of availability regarding vaccinated comparators for AZD1222 subjects. The availability of vaccinated comparators for AZD1222 subjects is expected to

be worse in the other data sources. Therefore, the analysis precision in other countries such as Spain, Italy, or the Netherlands is expected to be low.

- Regarding **duration of follow-up**, active comparators should have a follow-up duration that is at least as long as that for the AZD1222 cohort. However, it is possible that the AZD1222 cohort will have a shorter follow-up because AZD1222 use in Europe was stopped, and other COVID-19 vaccines were used as boosters. A short duration of follow-up among subjects in the AZD1222 cohorts may limit the evaluation of AESIs with unknown risk windows even if active comparators have longer durations of follow-up, ie, irrespective of the comparator used.
- Regarding **confounding and selection bias**, although there is a high risk of confounding by indication or channelling bias (ie, subjects of different ages and comorbidities were targeted by different vaccines and time periods during the vaccination campaigns), this risk of confounding would be attenuated by matching on calendar time. Moreover, additional attenuation would be expected by also matching on age and adjusting for potential risk factors and/or indicators of health status in the propensity score models.

Therefore, for interim report 2, the marketing authorisation holder proposes to implement the analysis as planned in the protocol and the SAP (ie, use of concurrent unvaccinated comparators). Additionally, feasibility counts of active comparators focusing on key matching variables in the AZD1222 PASS (eg, age, sex, and calendar time) will be also included.

11.3.3 Timing and Type of Second and Third Doses of Any COVID-19 Vaccine (AZD1222 or Other) Over the Study Period Among Subjects Who Received a First Dose of AZD1222

The description of the timing and type of second dose must be interpreted with caution given the relatively short duration of the study period included in interim report 1 and that this varied by data source, ranging from 4 months in SIDIAP and PHARMO to 9.5 months in CPRD. The fact that in SIDIAP and PHARMO only 54.5% and 27.8% of the subjects, respectively, had a second dose of any COVID-19 vaccine is likely due to not having enough study period to observe a second dose. This is further supported by the fact that in CPRD and ARS Toscana, which had longer study periods, 92.7% and 96.5% of the subjects, respectively had a second dose of any COVID-19 vaccine. In all data sources, when a second dose was observed, the second dose was AZD1222 in more than 95% of the subjects, and the rest were most often Pfizer-BioNTech COVID-19 vaccine, with very few subjects receiving other COVID-19 vaccines as the second dose. The timing between first and second doses varied only slightly by country and was most frequently 9 to 12 weeks, which is in line with recommendations [35].

In the EU data sources, very few (< 0.01%) or no subjects had a third dose of a COVID-19 vaccine among subjects with a first and a second dose of AZD1222. When a third dose was

observed, recording errors cannot be discarded based on the short time window observed between second and third doses and given that some third doses were with AZD1222, which was not indicated as booster. In CPRD, third doses where observed in less than 3% of the subjects with a first and second dose of AZD1222, and 98% of those third doses were with Pfizer-BioNTech COVID-19 vaccine. Timing between the second dose of AZD1222 and a third dose as the Pfizer-BioNTech COVID-19 vaccine was around 26 weeks, which is in line with UK roll-out of boosters. The median time between second dose and third dose of AZD1222 among the very few subjects (1.5%) with 3 doses of AZD1222 was 8.6 weeks, which in line with the UK Department of Health and Social Care and MHRA recommendation of administering a third dose at least 8 weeks after a second dose and only when potential benefits outweigh any potential risk [36]. It is possible that a third dose was administered to immunocompromised subjects.

In PHARMO, as described in Section 9.4.1.5, in the process of data cleaning, heterologous schemes were set to have unknown manufacturer. For this reason, no second doses of vaccines other than AZD1222 were observed in the study results. Similarly, because heterologous schemes were not identified and because AZD1222 was not indicated as a booster, no subjects with a third dose of any vaccine were identified in PHARMO.

11.3.4 Incidence Rates of Prespecified AESIs

Overall, no major differences were observed between the *all vaccinated population*, the AZD1222 vaccinated matched cohort, and the unvaccinated matched cohort, except for some AESIs that had a higher incidence among vaccinated subjects. The IRs of TTS indicated that this AESI was very rare and varied by data source. The largest numerical difference between vaccinated and unvaccinated subjects was observed for the incidence of TTS, thrombocytopaenia with bleeding, anaphylaxis, and stress cardiomyopathy—for which the occurrence among vaccinated subjects was higher than among unvaccinated subjects—but this was not consistent across all data sources.

The IRs of the AESIs differed substantially by data source, despite using a CDM and common analytics. Although there could be real differences in the IRs of these events by country, most of this heterogeneity can be attributed to the type of data available in each data source and the coding systems used, as described in the Limitations, Section 11.2.

Two studies have evaluated, in a pre-pandemic period, the background rates of AESIs potentially associated with COVID-19 vaccination and can be used to contextualise findings. One is the ACCESS project that, as the current study, was performed within the European VAC4EU network using the ConcePTION CDM. ACCESS was a multidatabase dynamic cohort study conducted in 2021 and covering data from 2017 to 2020. This study included 10 data sources from 7 European countries (Denmark, Germany, France, Italy, the Netherlands, Spain, and the UK). Data sources contained health insurance data, hospitalisation record

linkage data, or data from GP; some of the data sources used in the current study were also used in ACCESS (ARS Toscana, CPRD, PHARMO, SIDIAP). In the final report, a total number of 45 million individuals were included [38]. The second study was also a multinational network cohort study including electronic health records and health claims data for 126.6 million subjects from 8 countries: Australia, France, Germany, Japan, the Netherlands, Spain, the UK, and the United States, mapped to the Observational Medical Outcomes Partnership (OMOP) CDM. This study included CPRD Aurum and SIDIAP data sources that are also included in the current study [23].Within this network, a derived study in European data sources including 38 million subjects assessed specifically the background rates of non-vaccine–induced TTS, which also included myocardial infarction and ischaemic stroke as thromboembolic events [5].

Another study by Pottegård et al [28] assessed the rates of cardiovascular and haemostatic events in the first 28 days after vaccination with the AZD1222 vaccine in Denmark and Norway and compared them with rates observed in the general populations. This was a population-based cohort study performed using nationwide healthcare registers in Denmark and Norway. The cohorts included 148,792 people in Denmark and 132,472 people in Norway aged 18 to 65 years who received a first vaccination with AZD1222 from 9 February 2021 to 11 March 2021. The general populations of Denmark (2016-2018) and Norway (2018-2019) served as comparator cohorts. Outcomes were ascertained using information from all inpatient stays and hospital outpatient clinic contacts (including emergency room visits) and included incident arterial events, venous thromboembolism, thrombocytopaenia/coagulation disorders, and bleeding among vaccinated people compared with expected rates [28].

In the current study, compared with the pre-pandemic results for VTE with thrombocytopaenia reported in ACCESS, the TTS events occurred in a younger population, and the IRs were higher in most data sources, except in PHARMO and in subjects in the unvaccinated cohort in CPRD. Both the results of this study and those reported in the ACCESS project showed lower IRs of TTS than the IRs reported by Burn et al [5], and this was attributed to the fact that in addition to diagnostic codes, Burn et al [5] also included platelet levels in the identification of thrombocytopaenia, and most of the events of thrombocytopenia were identified by platelet measurement records in both SIDIAP and CPRD GOLD. The definition for TTS used in the current study was different from prior studies as study code lists are refined over time.

For other AESIs, specific comments are integrated in the Key Results, Section 11.1.

11.4 Generalisability

Generalisability of the study findings depends on the category of the finding [4; 30]. Findings related to vaccine utilisation and subject characterisation apply to the subject populations included in the study (Catalonia in Spain, Tuscany in Italy, England in UK, and the

Netherlands). The AZD1222 vaccine was approved by the EMA and the UK MHRA to be used among adults of all ages; however, some restrictions were imposed in European countries that limited the population who received the vaccine (see Section 6).

This study provided insight into the situation during the pandemic period covered by interim analysis 1, where contact patterns depended on governmental rules and where these rules varied both from country to country and from period to period. Accordingly, it is challenging to generalise some results of the study to other countries and time periods. Vaccine coverage and distribution as ascertained in this study was in line with national and regional data [8; 24].

There were no major differences between the incidences of AESIs between the *all vaccinated population* and the AZD1222 vaccinated matched cohort. Results about the risk of AESIs among subjects vaccinated with AZD1222 should be generalisable to all adults in the UK, Spain, Italy, and the Netherlands and in countries with similar age and sex distributions, healthcare systems, and vaccination policies for COVID-19.

12. OTHER INFORMATION

None.

13. CONCLUSION

Results from interim analysis 1 are descriptive. Overall, more than 5.2 million subjects were vaccinated with AZD1222 and 22.5 million available, unvaccinated comparators could be matched in Spain, Italy, the Netherlands, and the UK. Among subjects who received a first dose of AZD1222, when a second dose was also observed, this was most frequently also AZD1222. Vaccine coverage and distribution was in line with national and regional data.

Duration of follow-up was short among both vaccinated and unvaccinated cohorts but especially among the unvaccinated cohort. This may limit the evaluation of AESIs with unknown risk windows, which require longer durations of follow-up. An evaluation of the availability of active comparators will be presented in interim report 2.

The crude incidences of the AESIs varied by data source. This can be attributed to differences in the type of data available and in the granularity of the coding systems rather than to true differences in the incidence of these AESIs between countries. The largest numerical differences between vaccinated and unvaccinated subjects were observed for the incidence of TTS, thrombocytopaenia with bleeding, anaphylaxis, and stress cardiomyopathy, but differences were not consistent across all data sources. Differences in the incidence of AESIs between vaccinated and unvaccinated subjects in this report should be interpreted with caution given the short study period included in this first data extraction and the lack of

standardisation or adjustment for potential confounders and potential differences in the baseline characteristics of the study cohorts, which is planned for future analyses.

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Appendix A List of Stand-Alone Documents

Appendix B Additional Information

B 1 Quality-Control Processes at Each Data Access Partner

CPRD, United Kingdom

The DSRU had information security policies in place to preserve the confidentiality, integrity, and availability of the organisation's systems and data by ensuring the following: the premises provided suitable physical and environmental security, all equipment was secure and protected against malicious software, the network could be accessed only by authorised staff, telecommunication lines to the premises were protected from interception by being routed overhead or underground, and personnel received training regarding security awareness. The study was be conducted according to the *Guideline on Good Pharmacovigilance Practices* (GVP) [10] and according to the ENCePP Code of Conduct [11]. Data quality was a high priority at the DSRU and was assured through a number of methods based on staff training, validated systems, error prevention, data monitoring, data cleaning, and documentation, including the following:

- Staff training on data processing standard operating procedures
- Data management plan for every research study outlining, eg, the legal basis for data collection, data flows, data access rights, data retention periods
- Routine data cleaning to screen for errors, missing values, and extreme values and diagnose their cause
- System process logs to document staff access and other items

VID, Valencia, Spain

After Ethical Review Board approval, raw data was extracted in text file format and underwent a data quality check. Data were stored on secure servers at FISABIO in accordance with Spanish and data protection requirements and ensuring that no identifiable data was stored longer than required.

All the procedures that were implemented for data collection, storage, protection, retention, and destruction complied with national and EU legislation. The research team stayed up to date with the detailed provisions of the EU General Data Protection Regulation, which came into force in May 2018, and which superseded national legislation within the 28 EU Member States.

As of 22 March 2022, FISABIO had not received all the data banks needed to perform the analysis; no information regarding dates of extraction for the data banks that are pending was available. Data from VID will be analysed as soon as they become available, and results will be shared with the EMA.

SIDIAP, Catalonia, Spain

Data quality processes were implemented at each phase of the data flow cycle. Quality-control checks were performed at the extraction and uploading steps. To assess data completeness, the elements present were described by geographical areas, registering physician, time, and the distribution function of values. Correctness was assessed by validity checks on outliers, out-of-range values, formatting errors, and logical date's incompatibilities. Completeness and correctness measures were used to inform decisions on the required transformations to improve data quality (eg, harmonisation, normalisation, clean-up) and data fitness for the purpose of specific research projects.

ARS Toscana, Tuscany, Italy

One or 2 researchers reviewed the study documents. ARS Toscana received data on a bimonthly basis from the Tuscany region, and these data then underwent a first QC. The ARS Toscana statistical office appended the data to an Oracle database and checks them using a dashboard to identify any inconsistencies with historical data.

The Pharmacoepidemiology Unit had standardised parametric procedures in Structured Query Language (SQL) and Stata to extract data from the Oracle database. Parametric procedures were also available to convert the data into various CDMs. Study-specific procedures were developed, based on the study protocol and/or SAP, as well as by composing standard parametric procedures in Stata. Standard procedures in R were under development in the context of the ConcePTION project. The unit also regularly generates simulated data sets and double programming in R programmes that were originally developed in SAS or Stata.

PHARMO, the Netherlands

PHARMO is ISO 9001:2015 certified for its quality management system. At the study level, all aspects of the study from protocol development to the reporting of the results were conducted within the work frame of the PHARMO quality management system.

The PHARMO Database Network combines data from different sources (eg, pharmacy, hospital, laboratory). These different sources were probabilistically linked through validated algorithms to ensure that subject privacy is maintained. Before databases were linked, those subjects for whom linkage-critical information (eg, date of birth, gender, GP) was missing were removed. All data were handled in a way that met the full requirements for managing and storing sensitive subject data. Involved researchers signed a confidentiality agreement. The anonymised data were stored on an internal network drive. Relevant extractions were stored in a project folder. Specific checks on the linked data were performed, depending on which data sources were used. The study data folder, including all extracted and derived data tables, were archived after study closure.

All programming was developed in accordance with standard operating procedures, prepared by the lead analyst, and reviewed/quality controlled by an experienced analyst at PHARMO. Additionally, all results and reports were audited by the QC department, using a standardised check list.

The use of the PHARMO data was controlled by the independent Compliance Committee STIZON/PHARMO Institute. The Compliance Committee STIZON/PHARMO Institute consists of representatives of the participating data suppliers and a privacy expert (chairman of this committee). Each study required permission from this committee, according to the applicable legislation in the Netherlands, eg, the Personal Data Protection Act and the Medical Treatment Contract Act. Within this legal framework, the Code of Conduct "Use of Data in Health Research" was an important document for the interpretation of the use of this kind of data for scientific research in the Netherlands and is approved by the Dutch Data Protection Authority (www.dutchdpa.nl).

UMCU

UMCU, as the scientific centre responsible for central data management and analysis, all documents underwent QC review and senior scientific review at UMCU. Data Management and statistical analysis followed standard operating procedures for UMCU. All statistical analysis programs were double coded by UMCU and RTI-HS, or code was reviewed. UMCU created clear documentation (graphical and in Excel spreadsheet) of the data management steps, beginning with describing the required variables from the CDM and each of the subsequent transformation steps and intermittent data tables. All R code that was required was written and versioned on GitHub and reviewed by a tester. RTI-HS doubled code (ie, scripts in SAS were developed independently, and the output from analysis programs in R and SAS was compared against each other to ensure consistency between them) or conducted code review (random matching programming) of the datasets built in R by UMCU using SAS and from instructions provided by UMCU. Discrepancies were resolved.

RTI Health Solutions

At RTI-HS, as the coordinating centre, all key study documents underwent QC review, senior scientific review, and editorial review. Senior reviewers with expertise in the appropriate subject matter area provided advice on the design of research study approaches and the conduct of the study and reviewed results, reports, and other key study documents. All key study documents, such as the analysis plan and study reports, underwent QC review, senior scientific review, and editorial review.

Procedures were consistent with the International Society for Pharmacoepidemiology (ISPE) *Guidelines for Good Pharmacoepidemiology Practices (GPP)* [21], and with the ENCePP *Guide on Methodological Standards in Pharmacoepidemiology* [12], the *ENCePP Code of*

Conduct [11] and the EMA *Guideline on Good Pharmacovigilance Practices (GVP). Module VIII – Post-authorisation safety studies* (EMA/813938/2011 Rev 3) [10].

See UMCU section for details of the programming and analytic role of RTI-HS.

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Table 1.1.CPRD. Baseline Characteristics Among the *All Vaccinated Population*, AZD1222 Cohort

	Over all the study period included in interim report 1	
	N	%[a]
Totals	4,171,486	100.00%
Calendar quarter at index date		
Q1 2021	3,461,321	82.98%
Q2 2021	686,535	16.46%
Q3 2021	23,497	0.56%
Q4 2021	133	<0.01%
Q1 2022	0	0.00%
Q2 2022	0	0.00%
Duration of lookback period (years)		
Mean (SD)	14.99	(9.23)
Median (Q1, Q3)	15	(6,26)
Age at index date (years)		
Mean (SD)	54.40	(14.80)
Median (Q1, Q3)	54	(45,65)
Age groups (years)		
0-11	16	<0.01%
12-15	161	<0.01%
16-19	31,096	0.75%
20-29	201,817	4.84%
30-39	357,360	8.57%
40-49	943,790	22.62%
50-59	1,144,770	27.44%
60-69	801,556	19.22%
70-79	530,554	12.72%
80+	160,366	3.84%
Sex, female	2,133,070	51.13%
COVID-19 history (diagnosis or test)	403,574	9.67%

N, number; Q1, quartile 1; Q3, quartile 3; SD, standard deviation.
[a] Counts and percentages, unless otherwise specified.

Table 2.1.CPRD. Incidence Rates or Prevalence Proportions of AESIs With Well-Defined Risk Window and Cumulative Incidence (1 − KM) of AESIs With Unknown Risk Window Among the *All Vaccinated Population*

		All AZD1222 vaccinated population				
AESI (risk window, days)	**Risk esti-mator**	**N Subjects**	**N Out-comes**	**Person-years**	**Risk per 10,000**	**95% CI**
Myasthenia gravis[a] (1-365)	1-KM	4,166,289	204	2,432,345.1	0.67	(0.00-6.63)
Thrombosis without thrombocytopenia[b] (1-42)	IR	4,166,789	22	916,524.7	0.24	(0.15-0.36)
Thrombosis with thrombocytopenia syndrome[b] (1-42)	IR	4,166,842	16	916,536.7	0.17	(0.10-0.28)
Narcolepsy[b] (1-42)	IR	4,166,735	24	916,511.5	0.26	(0.17-0.39)
Thrombocytopenia with associated bleeding[b] (1-42)	IR	4,166,838	6	916,536.5	0.07	(0.02-0.14)
Autoimmune thyroiditis[a] (1-180)	1-KM	4,164,676	932	2,398,657.6	2.54	(0.00-8.50)
Acute aseptic arthritis[b] (1-42)	IR	4,129,759	7,918	907,213.2	87.28	(85.37-89.22)
Guillain-Barré syndrome[b] (1-42)	IR	4,166,702	42	916,502.6	0.46	(0.33-0.62)
Thrombocytopenia[b] (1-42)	IR	4,164,511	632	915,948.5	6.90	(6.37-7.46)
Capillary leak syndrome[a] (1-365)	1-KM	4,166,857	[redacted]	[redacted]	0.00	(0.00-5.96)
Postural orthostatic tachycardia syndrome[b] (1-42)	IR	4,166,590	56	916,472.2	0.61	(0.46-0.79)
Acute cardiac injury including microangiopathy, cardiogenic shock, heart failure[b] (1-90)	IR	4,149,169	7,490	1,778,312.5	42.12	(41.17-43.08)
Stress cardiomyopathy[b] (1-42)	IR	4,166,697	44	916,501.0	0.48	(0.35-0.64)
Myocardial infarction[b] (1-28)	IR	4,156,593	1,339	610,560.1	21.93	(20.77-23.14)
Myocarditis/Pericarditis[b] (1-42)	IR	4,165,936	186	916,313.2	2.03	(1.75-2.34)
Acute pancreatitis[a] (1-365)	1-KM	4,163,384	1,673	2,430,160.7	5.17	(0.00-11.13)
Acute kidney injury[b] (1-14)	IR	4,151,602	1,000	305,313.8	32.75	(30.75-34.85)
Acute liver injury[b] (1-14)	IR	4,165,850	66	306,447.7	2.15	(1.67-2.74)
Multiple sclerosis, and other demyelinating disorders[a] (1-365)	1-KM	4,161,876	1,351	2,429,264.3	3.83	(0.00-9.79)
Transverse myelitis[b] (1-90)	IR	4,166,710	48	1,787,183.6	0.27	(0.20-0.36)
Encephalitis (including ADEM)[b] (1-42)	IR	4,166,733	43	916,507.4	0.47	(0.34-0.63)

		All AZD1222 vaccinated population				
AESI (risk window, days)	Risk esti-mator	N Subjects	N Out-comes	Person-years	Risk per 10,000	95% CI
Other peripheral and polyneuropathies[b] (1-42)	IR	4,164,668	499	915,993.8	5.45	(4.98-5.95)
Generalised convulsions[b] (0-14)	IR	4,160,935	532	327,905.5	16.22	(14.87-17.66)
Optic neuritis/neuromyelitis optica spectrum disorder[b] (1-42)	IR	4,166,619	54	916,480.8	0.59	(0.44-0.77)
Bell's palsy[b] (1-42)	IR	4,164,896	497	916,040.8	5.43	(4.96-5.92)
Fibromyalgia[a] (91-365)	1-KM	3,907,143	1,233	675,209.0	8.32	(2.09-14.54)
Chronic fatigue syndrome/ME/PVFS[a] (183-365)	1-KM	517,060	8	29,609.7	0.47	(0.00-15.94)
Anosmia, ageusia[a] (1-365)	1-KM	4,157,226	2,408	2,426,526.4	7.79	(1.81-13.76)
Type III hypersensitivity reactions[a] (1-365)	1-KM	4,149,370	5,845	2,419,777.2	19.60	(13.33-25.86)
Anaphylaxis[c] (0-2)	PP	4,166,271	71	65,731.5	0.17	(0.13-0.21)
Rhabdomyolysis[b] (1-42)	IR	4,166,505	86	916,456.3	0.94	(0.75-1.16)
Multisystem inflammatory syndrome in adults/children[b] (1-42)	IR	4,166,858	0	916,541.3	0.00	(0.00-0.04)
Sudden death[c] (0-6)	PP	4,167,245	[redacted]	[redacted]	0.00	(0.00-0.01)
Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease, including ARDS[a] (14-365)	1-KM	4,157,995	308	2,284,194.9	0.98	(0.00-4.99)
ARDS[b] (1-28)	IR	4,166,309	54	612,140.8	0.88	(0.66-1.15)
Erythema multiforme[a] (1-365)	1-KM	4,166,672	99	2,432,639.5	0.31	(0.00-6.26)
Chilblain-like skin lesions[a] (1-365)	1-KM	4,165,656	398	2,431,894.8	1.00	(0.00-6.96)

ADEM, acute disseminated encephalomyelitis; AESI, adverse event of special interest; ARDS, acute respiratory distress syndrome; CI, confidence interval; IR, incidence rate; KM, Kaplan-Meier; ME, myalgic encephalitis; N, number; NA, not available; PR, prevalence rate; PVFS, postviral fatigue syndrome; PY, person-years.

[a] Cumulative incidence (1-KM) per 10,000, for these outcomes with unknown risk windows

[b] Incidence rate (IR) per 10,000 person-years, for outcomes with well-defined risk windows

[c] Prevalence proportion (PP) per 10,000, for outcomes with well-defined and very short risk windows

Table 2.CPRD. TTS. Cumulative Incidence (1 − KM) of Thrombosis With Thrombocytopenia Syndrome Among the *All Vaccinated Population*, by Age Groups and Sex

	All AZD1222 vaccinated population				
	N Subjects	N Outcomes	Person-years	1-KM per 10,000	95% CI
By age groups (years)					
0-11	16	0	2.3	0.00	(0.00-1854.50)
12-15	161	0	32.3	0.00	(0.00-928.79)
16-19	31,068	0	6,772.0	0.00	(0.00-77.04)
20-29	201,254	[redacted]	[redacted]	0.20	(0.00-30.47)
30-39	356,597	[redacted]	[redacted]	0.03	(0.00-22.77)
40-49	942,493	5	206,401.1	0.05	(0.00-14.04)
50-59	1,143,755	[redacted]	[redacted]	0.03	(0.00-12.73)
60-69	801,065	[redacted]	[redacted]	0.04	(0.00-15.21)
70-79	530,327	0	115,621.4	0.00	(0.00-18.65)
80+	160,106	0	34,100.2	0.00	(0.00-33.94)
By sex					
Male	2,035,710	9	447,818.6	0.04	(0.00-9.56)
Female	2,131,079	7	468,706.5	0.03	(0.00-9.34)

CI, confidence interval; KM, Kaplan-Meier; N, number; PY, person-years.
[a] Numbers correspond to counts and percentages unless otherwise specified.

Table 3.1.CPRD. Description of the Utilisation Pattern of Subsequent Doses of a COVID-19 Vaccine in the *All Vaccinated First Dose Population*, Over All the Study Period, AZD1222 cohort

	Over all the study period included in interim report 1[a]	
	N	%
Subjects with a first dose of AZD1222 (Vaxzevria)	4,161,752	
Subjects who had received only a first dose of AZD1222 at the end of study period for interim report 1	304,519	7.32%
Subjects with a first dose of AZD122 who receive a second dose of any COVID-19 vaccine and time between doses	3,857,233	92.68%
Vaxzevria (COVID-19 Vaccine AstraZeneca)	3,840,711	92.29%
Time between dose 1 and dose 2, weeks		
Mean (SD)	10.61	(1.76)
Median (Q1-Q3)	11.0	(9.7, 11.3)
min, max	2,	39
<2 weeks	0	0.00%
2-4 weeks	12,506	0.33%
5-8 weeks	513,513	13.37%
9-12 weeks	3,150,506	82.03%
13-18 weeks	146,742	3.82%
>18 weeks	17,444	0.45%
Comirnaty (COVID-19 Vaccine Pfizer-BioNTech)	15,617	0.38%
Time between dose 1 and dose 2, weeks		
Mean (SD)	15.87	(8.93)
Median (Q1-Q3)	11.4	(10.3, 20.1)
min, max	2,	39
<2 weeks	0	0.00%
2-4 weeks	235	1.50%
5-8 weeks	2,003	12.83%
9-12 weeks	7,254	46.45%
13-18 weeks	1,992	12.76%
>18 weeks	4,133	26.46%

	Over all the study period included in interim report 1[a]	
	N	%
Spikevax (COVID-19 Vaccine Moderna)	904	0.02%
Time between dose 1 and dose 2, weeks		
Mean (SD)	11.60	(4.58)
Median (Q1-Q3)	10.9	(9.0, 11.7)
min, max	2,	34
<2 weeks	0	0.00%
2-4 weeks	13	1.44%
5-8 weeks	174	19.25%
9-12 weeks	557	61.62%
13-18 weeks	94	10.40%
>18 weeks	66	7.30%
COVID-19 Vaccine Janssen	[redacted]	
Time between dose 1 and dose 2, weeks		
Mean (SD)	22.43	(.)
Median (Q1-Q3)	22.4	(22.4, 22.4)
min, max	22,	22
<2 weeks	0	0.00%
2-4 weeks	0	0.00%
5-8 weeks	0	0.00%
9-12 weeks	0	0.00%
13-18 weeks	0	0.00%
>18 weeks	[redacted]	
Other COVID-19 vaccines	0	0.00%
Time between dose 1 and dose 2, weeks		
Mean (SD)		
Median (Q1-Q3)		
min, max		
<2 weeks	0	0.00%
2-4 weeks	0	0.00%
5-8 weeks	0	0.00%
9-12 weeks	0	0.00%
13-18 weeks	0	0.00%
>18 weeks	0	0.00%

	Over all the study period included in interim report 1[a]	
	N	%
Subjects with a first and second dose of AZD122 who receive a third dose of any COVID-19 vaccine and time between doses	105,784	2.75%
Vaxzevria (COVID-19 Vaccine AstraZeneca)	1,616	0.04%
Time between dose 2 and dose 3		
Mean (SD)	10.82	(7.69)
Median (Q1-Q3)	8.6	(4.9, 14.0)
min, max	2,	34
<12 weeks	1,127	69.74%
12-24 weeks	322	19.93%
25-37 weeks	167	10.33%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%
Comirnaty (COVID-19 Vaccine Pfizer-BioNTech)	104,070	2.71%
Time between dose 2 and dose 3		
Mean (SD)	26.23	(2.28)
Median (Q1-Q3)	26.6	(26.0, 27.3)
min, max	2,	36
<12 weeks	163	0.16%
12-24 weeks	13,964	13.42%
25-37 weeks	89,943	86.43%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%
Spikevax (COVID-19 Vaccine Moderna)	97	<0.01%
Time between dose 2 and dose 3		
Mean (SD)	21.45	(7.37)
Median (Q1-Q3)	26.0	(16.9, 26.6)
min, max	3,	31
<12 weeks	16	16.49%
12-24 weeks	25	25.77%
25-37 weeks	56	57.73%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%

	Over all the study period included in interim report 1[a]	
	N	%
COVID-19 Vaccine Janssen	[redacted]	
Time between dose 2 and dose 3		
Mean (SD)	[redacted]	
Median (Q1-Q3)	[redacted]	
min, max	[redacted]	
<12 weeks	[redacted]	
12-24 weeks	[redacted]	
25-37 weeks	0	0.00%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%
Other COVID-19 vaccines	0	0.00%
Time between dose 2 and dose 3		
Mean (SD)		
Median (Q1-Q3)		
min, max		
<12 weeks	0	0.00%
12-24 weeks	0	0.00%
25-37 weeks	0	0.00%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%

Q1 = Quartile 1; Q3 = Quartile 3; SD = Standard deviation

Table 4.CPRD. Cohort Attrition for the *Matched Population*

Cohort	N	(%)
AZD1222 cohort		
All vaccinated population	4,171,486	
All vaccinated first dose population	4,161,752	(99.77%)
And with at least 12 months lookback period (eligible to be matched)	4,057,222	(97.49%)
Unique vaccinated subjects not matched	16,635	(0.41%)
Unique vaccinated subjects matched	4,040,587	(99.59%)
Matching ratio 1:1	19,305	(0.48%)
Matching ratio 1:2	19,689	(0.49%)
Matching ratio 1:3	19,392	(0.48%)
Matching ratio 1:4	20,214	(0.50%)
Matching ratio 1:5	3,961,987	(98.05%)
Unvaccinated cohort		
Unique subjects with no record of vaccination with any COVID-19 vaccine during the study period	12,823,272	
And with at least 12 months lookback period (eligible to be matched)	12,683,746	(98.91%)
Unique unvaccinated subjects matched	5,762,912	(45.44%)
Unique unvaccinated subjects not matched	6,920,834	(54.56%)
Non-unique unvaccinated subjects matched	20,007,650	
Number of times an unvaccinated subject was matched		
Median (Q1-Q3)	2	(1-5)
Min-Max		1-103
1	2,020,199	(35.06%)
2	1,111,848	(19.29%)
3	691,903	(12.01%)
4	480,640	(8.34%)
5 or more	1,458,322	(25.31%)

N = number; Q1 = Quartile 1; Q3 = Quartile 3

Table 5.CPRD. Reasons for Censoring Follow-up Among the *Matched Population* Cohorts

	AZD1222 cohort		Unvaccinated cohort	
Cohort design	**N**	**(%)**	**N**	**(%)**
Total	4,040,587	(100.00%)	20,007,650	(100.00%)
Person-months of follow-up				
Mean follow-up (SD), months	6.98	(1.32)	2.56	(2.79)
Median follow-up (Q1-Q3), months	7.1	(6.6-8.0)	1.1	(0.2-5.2)
P1 - P99 follow-up, months	1.8	- 8.9	<0.1	- 8.5
Received AZD1222, n (%)	0	(0.00%)	10,101,685	(50.49%)
Received any COVID-19 vaccine other than AZD1222, n (%)	116,439	(2.88%)	3,904,867	(19.52%)
Censored 365 days after the second dose of AZD1222, n (%)	0	(0.00%)	0	(0.00%)
End of study period, n (%)	2,623,696	(64.93%)	3,782,569	(18.91%)
Enrolment termination date in the health plan or system[a], n(%)	1,274,442	(31.54%)	2,155,264	(10.77%)
Death, n(%)	26,010	(0.64%)	63,265	(0.32%)

[a] Enrolment termination date in the health system or database: Please note that in the first interim report, for enrolment termination date in the database, no differentiation was made between whether the last collection date of each general practice represented actual disenrollment from CPRD Aurum or whether it represented an earlier data cut date, prior to 13 October 2021 (latest practice last collection date).
N = number; Q1 = Quartile 1; Q3 = Quartile 3

Table 11.1.CPRD. Crude Risk Estimates for AESIs in the *Matched Cohorts* Based on Definition and Duration of Risk Windows

		AZD1222 cohort					Unvaccinated cohort				
AESI (risk window, days)	**Risk estimator**	**N Patients**	**N Outcomes**	**Person-years**	**Risk per 10,000**	**95% CI**	**N Patients**	**N Outcomes**	**Person-years**	**Risk per 10,000**	**95% CI**
Myasthenia gravis[a] (1-365)	1-KM	4,039,620	201	2,359,663.8	0.69	(0.00-6.73)	19,992,067	129	4,283,194.2	0.17	(0.00-2.89)
Thrombosis without thrombocytopenia[b] (1-42)	IR	4,040,105	22	889,776.4	0.25	(0.15-0.37)	19,995,690	27	2,111,576.4	0.13	(0.05-0.31)
Thrombosis with thrombocytopenia syndrome[b] (1-42)	IR	4,040,158	15	889,788.5	0.17	(0.09-0.28)	19,996,171	[redacted]		0.01	(0.00-0.04)
Narcolepsy[b] (1-42)	IR	4,040,054	23	889,764.1	0.26	(0.16-0.39)	19,995,120	59	2,111,475.8	0.28	(0.15-0.53)
Thrombocytopenia with associated bleeding[b] (1-42)	IR	4,040,151	6	889,787.5	0.07	(0.02-0.15)	19,996,083	[redacted]		0.01	(0.00-0.04)
Autoimmune thyroiditis[a] (1-180)	1-KM	4,038,089	899	2,327,372.4	2.53	(0.00-8.58)	19,976,869	1,571	4,242,132.1	4.53	(0.00-9.73)
Acute aseptic arthritis[b] (1-42)	IR	4,004,019	7,680	880,694.9	87.20	(85.26-89.18)	19,689,947	8,811	2,085,954.4	42.24	(40.12-44.47)
Guillain-Barré syndrome[b] (1-42)	IR	4,040,024	41	889,755.7	0.46	(0.33-0.63)	19,994,830	48	2,111,473.9	0.23	(0.12-0.42)
Thrombocytopenia[b] (1-42)	IR	4,037,933	604	889,225.3	6.79	(6.26-7.36)	19,977,042	1,034	2,109,766.1	4.90	(4.23-5.67)
Capillary leak syndrome[a] (1-365)	1-KM	4,040,170	[redacted]		0.00	(0.00-6.05)	19,996,272	0	4,283,916.0	0.00	(0.00-2.72)
Postural orthostatic tachycardia syndrome[b] (1-42)	IR	4,039,918	55	889,727.2	0.62	(0.47-0.80)	19,994,256	78	2,111,335.2	0.37	(0.25-0.54)

AESI (risk window, days)	Risk estimator	AZD1222 cohort					Unvaccinated cohort				
		N Patients	N Outcomes	Person-years	Risk per 10,000	95% CI	N Patients	N Outcomes	Person-years	Risk per 10,000	95% CI
Acute cardiac injury including microangiopathy, cardiogenic shock, heart failure[b] (1-90)	IR	4,023,444	7,096	1,726,611.5	41.10	(40.15-42.07)	19,856,850	8,306	3,514,032.6	23.64	(22.24-25.13)
Stress cardiomyopathy[b] (1-42)	IR	4,040,015	44	889,753.0	0.49	(0.36-0.66)	19,994,905	43	2,111,527.1	0.20	(0.10-0.41)
Myocardial infarction[b] (1-28)	IR	4,030,354	1,295	592,744.4	21.85	(20.67-23.07)	19,911,948	2,836	1,515,385.4	18.71	(17.13-20.45)
Myocarditis/Pericarditis[b] (1-42)	IR	4,039,292	180	889,574.3	2.02	(1.74-2.34)	19,989,186	335	2,110,865.6	1.59	(1.27-1.98)
Acute pancreatitis[a] (1-365)	1-KM	4,036,810	1,609	2,357,546.4	5.15	(0.00-11.21)	19,967,621	2,090	4,277,903.0	3.35	(0.60-6.10)
Acute kidney injury[b] (1-14)	IR	4,025,712	949	296,416.0	32.02	(30.01-34.12)	19,885,730	2,539	846,846.9	29.98	(27.66-32.50)
Acute liver injury[b] (1-14)	IR	4,039,214	60	297,496.3	2.02	(1.54-2.60)	19,988,478	183	851,077.7	2.15	(1.57-2.95)
Multiple sclerosis, and other demyelinating disorders[a] (1-365)	1-KM	4,035,406	1,310	2,356,716.2	3.83	(0.00-9.88)	19,960,542	1,484	4,276,481.1	2.73	(0.00-5.53)
Transverse myelitis[b] (1-90)	IR	4,040,030	47	1,735,056.0	0.27	(0.20-0.36)	19,995,154	62	3,532,146.2	0.18	(0.10-0.32)
Encephalitis (including ADEM)[b] (1-42)	IR	4,040,051	42	889,759.9	0.47	(0.34-0.64)	19,995,340	61	2,111,528.3	0.29	(0.17-0.49)

AESI (risk window, days)	Risk estimator	AZD1222 cohort					Unvaccinated cohort				
		N Patients	N Outcomes	Person-years	Risk per 10,000	95% CI	N Patients	N Outcomes	Person-years	Risk per 10,000	95% CI
Other peripheral and polyneuropathies[b] (1-42)	IR	4,038,055	474	889,263.6	5.33	(4.86-5.83)	19,978,676	556	2,110,042.4	2.64	(2.15-3.24)
Generalised convulsions[b] (0-14)	IR	4,034,714	495	318,349.4	15.55	(14.21-16.98)	19,959,334	1,077	922,341.3	11.68	(10.39-13.12)
Optic neuritis/neuromyelitis optica spectrum disorder[b] (1-42)	IR	4,039,946	49	889,735.4	0.55	(0.41-0.73)	19,994,430	110	2,111,391.5	0.52	(0.34-0.80)
Bell's palsy[b] (1-42)	IR	4,038,250	484	889,301.5	5.44	(4.97-5.95)	19,979,411	778	2,109,832.0	3.69	(3.18-4.28)
Fibromyalgia[a] (91-365)	1-KM	2,580,058	768	414,765.0	8.74	(1.11-16.38)	5,239,865	1,006	766,002.1	5.06	(0.00-10.40)
Chronic fatigue syndrome/ME/PVFS[a] (183-365)	1-KM	240,166	5	15,402.2	0.56	(0.00-22.74)	400,464	[redacted]	[redacted]	0.70	(0.00-18.30)
Anosmia, ageusia[a] (1-365)	1-KM	4,030,880	2,334	2,354,052.7	7.81	(1.74-13.88)	19,924,029	4,118	4,266,787.0	9.60	(3.48-15.72)
Type III hypersensitivity reactions[a] (1-365)	1-KM	4,023,228	5,654	2,347,481.6	19.71	(13.29-26.13)	19,861,070	4,959	4,260,064.0	7.75	(5.01-10.49)
Anaphylaxis[c] (0-2)	PP	4,039,648	66	63,811.8	0.16	(0.13-0.21)	19,999,863	153	216,492.9	0.08	(0.06-0.09)
Rhabdomyolysis[b] (1-42)	IR	4,039,850	84	889,714.1	0.94	(0.75-1.17)	19,993,554	176	2,111,356.7	0.83	(0.60-1.16)
Multisystem inflammatory syndrome in adults/children[b] (1-42)	IR	4,040,171	0	889,792.4	0.00	(0.00-0.04)	19,996,278	0	2,111,630.9		NR
Sudden death[c] (0-6)	PP	4,040,587	[redacted]	[redacted]	0.00	(0.00-0.01)	20,007,650	[redacted]	[redacted]	0.00	(0.00-0.00)

AESI (risk window, days)	Risk estimator	AZD1222 cohort					Unvaccinated cohort				
		N Patients	N Outcomes	Person-years	Risk per 10,000	95% CI	N Patients	N Outcomes	Person-years	Risk per 10,000	95% CI
Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease, including ARDS[a] (14-365)	1-KM	3,744,673	0	2,043,037.8	0.00	(0.00-4.11)	12,888,648	0	3,706,533.3	0.00	(0.00-2.21)
ARDS[b] (1-28)	IR	4,039,641	53	594,262.0	0.89	(0.67-1.17)	19,991,953	185	1,520,344.4	1.22	(0.88-1.69)
Erythema multiforme[a] (1-365)	1-KM	4,039,990	95	2,359,949.4	0.31	(0.00-6.35)	19,994,697	117	4,283,560.8	0.20	(0.00-2.92)
Chilblain-like skin lesions[a] (1-365)	1-KM	4,039,029	386	2,359,240.0	1.01	(0.00-7.05)	19,986,412	679	4,281,911.4	0.58	(0.00-3.30)

ADEM, acute disseminated encephalomyelitis; AESI, adverse event of special interest; ARDS, acute respiratory distress syndrome; CI, confidence interval; IR, incidence rate; KM, Kaplan-Meier; ME, myalgic encephalitis; N, number; NA, not available; NR, not reportable; PR, prevalence rate; PVFS, postviral fatigue syndrome; PY, person-years.

[a] Cumulative incidence (1-KM) per 10,000, for these outcomes with unknown risk windows.

[b] Incidence rate (IR) per 10,000 person-years, for outcomes with well-defined risk windows.

[c] Prevalence proportion (PP) per 10,000, for outcomes with well-defined and very short risk windows.

Figure1.CPRD. Number of Subjects Vaccinated With a First Dose of AZD1222 Who Were Excluded, Included, and Could Be Matched by Calendar Time

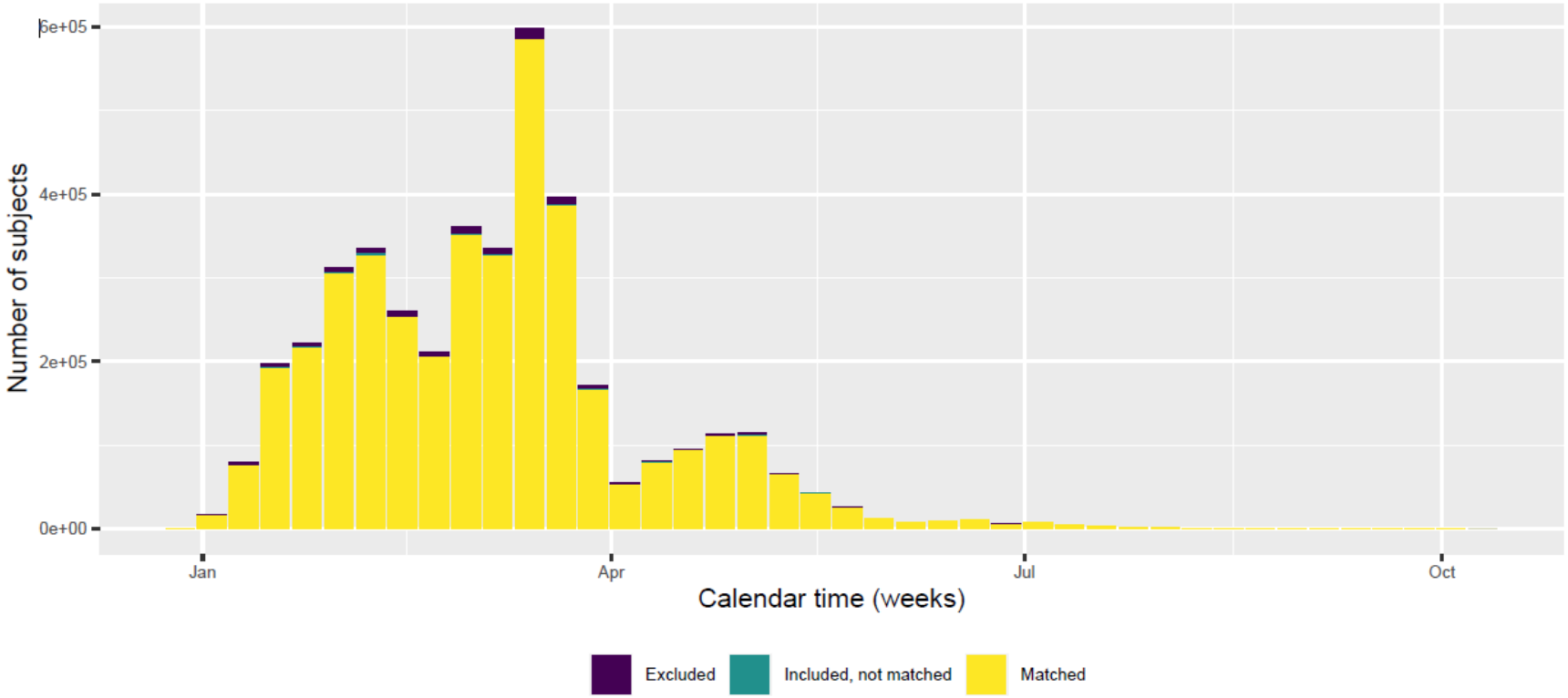


Figure2.CPRD. AZD1222 Cohort, Reasons for Censoring Follow-up, by Quarter

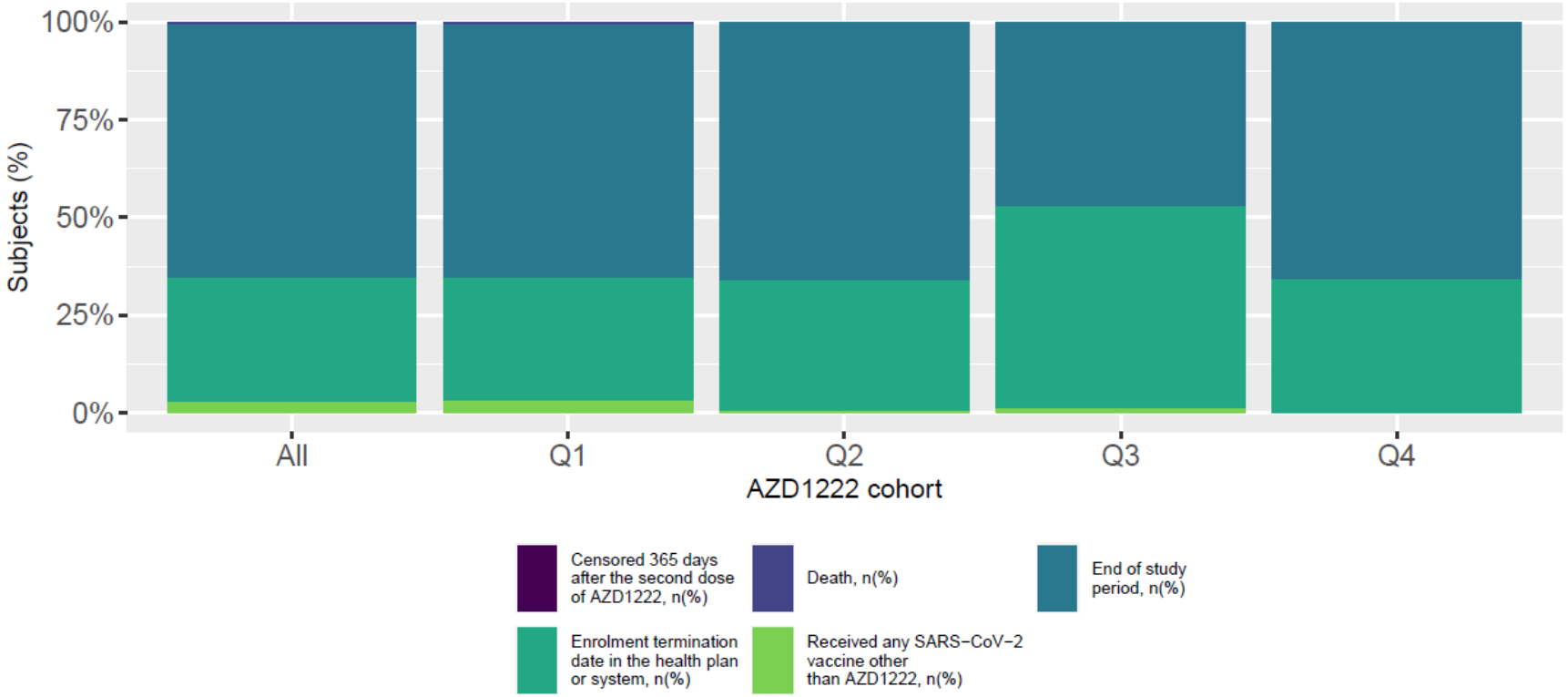


Figure2.CPRD. Unvaccinated Cohort, Reasons for Censoring Follow-up, by Quarter

Figure 5.CPRD. Myasthenia Gravis, Cumulative Incidence With Unknown Risk Window

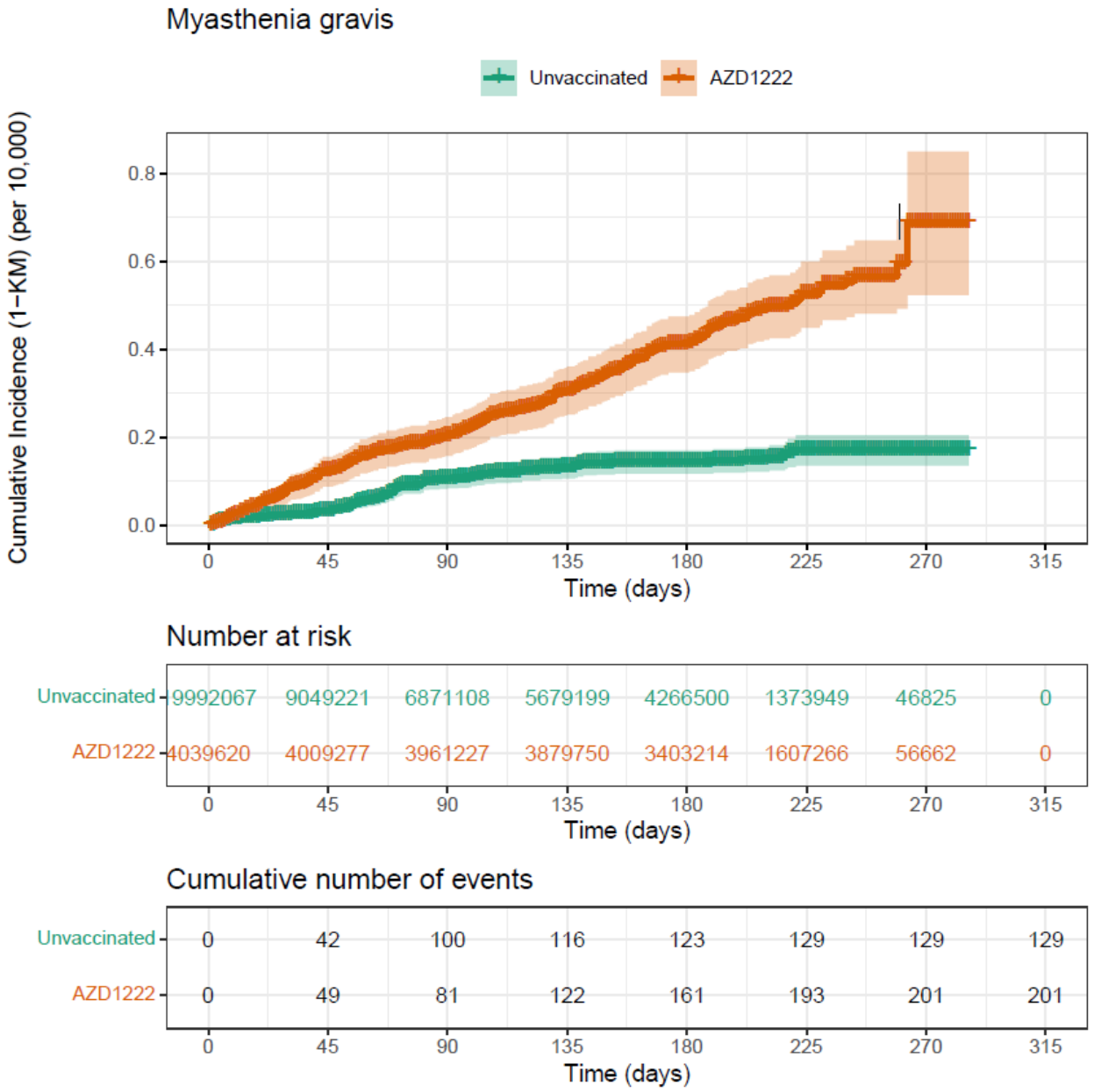


Figure 5.CPRD. Autoimmune Thyroiditis, Cumulative Incidence With Unknown Risk Window

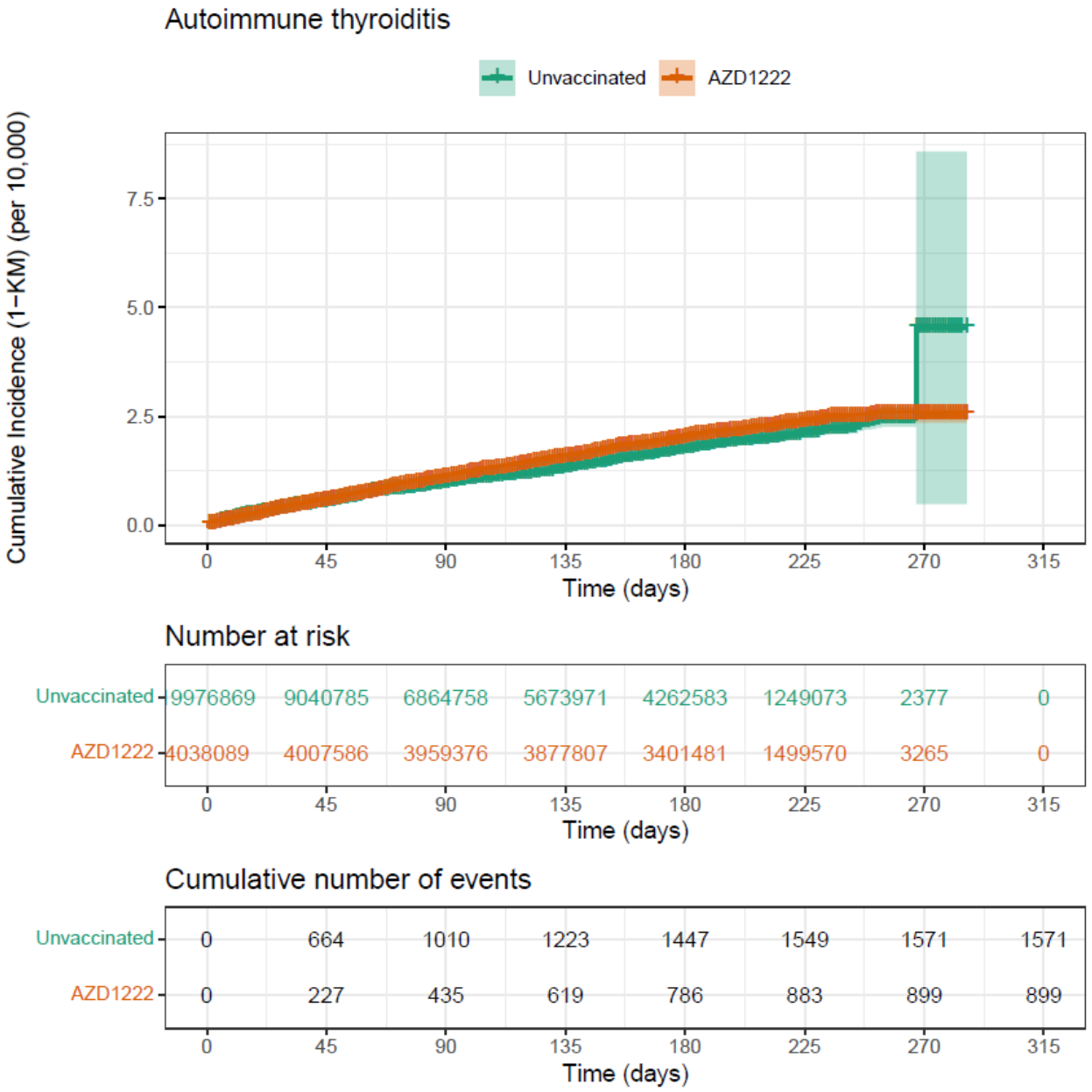


Figure 5.CPRD. Capillary Leak Syndrome, Cumulative Incidence With Unknown Risk Window

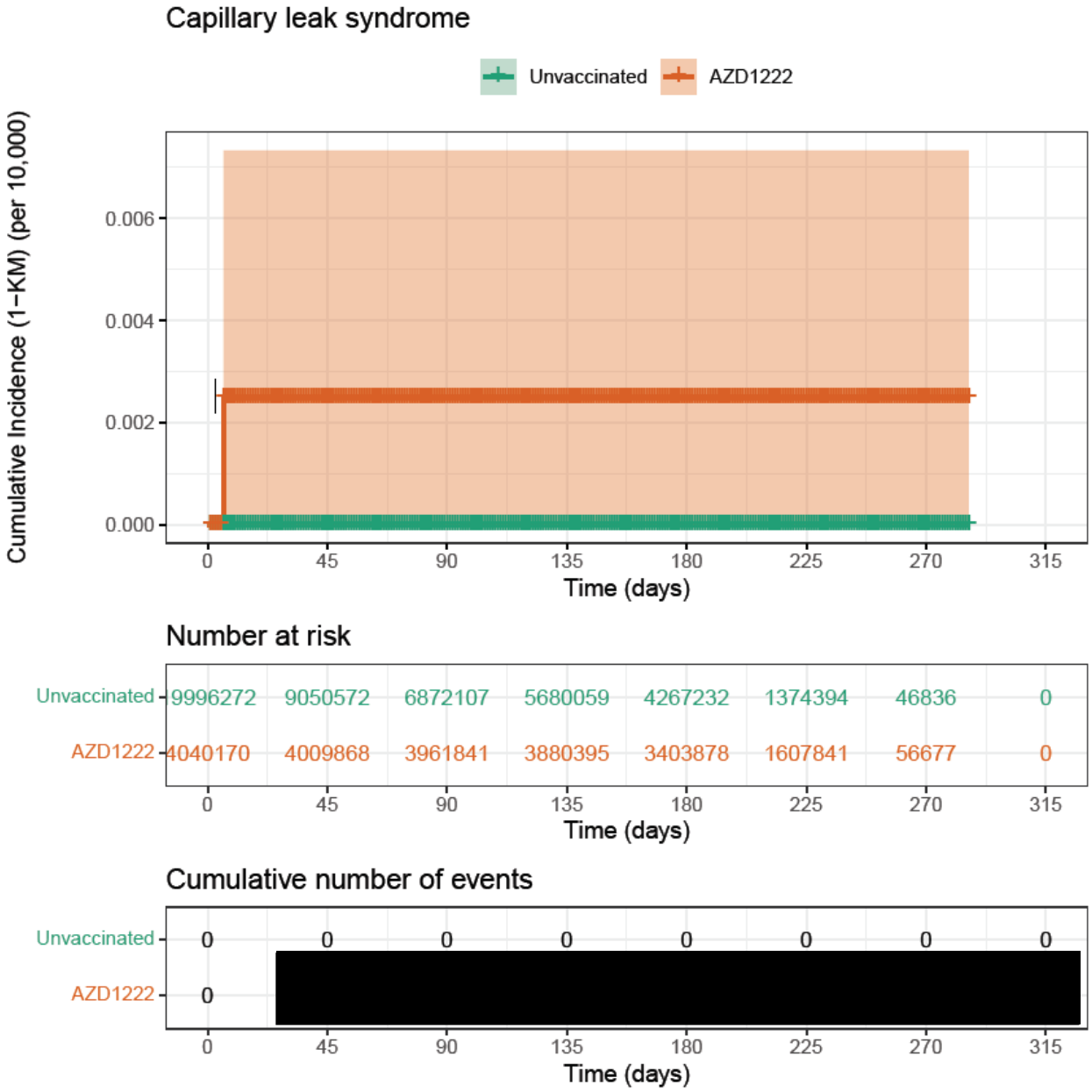


Figure 5.CPRD. Acute Pancreatitis, Cumulative Incidence With Unknown Risk Window

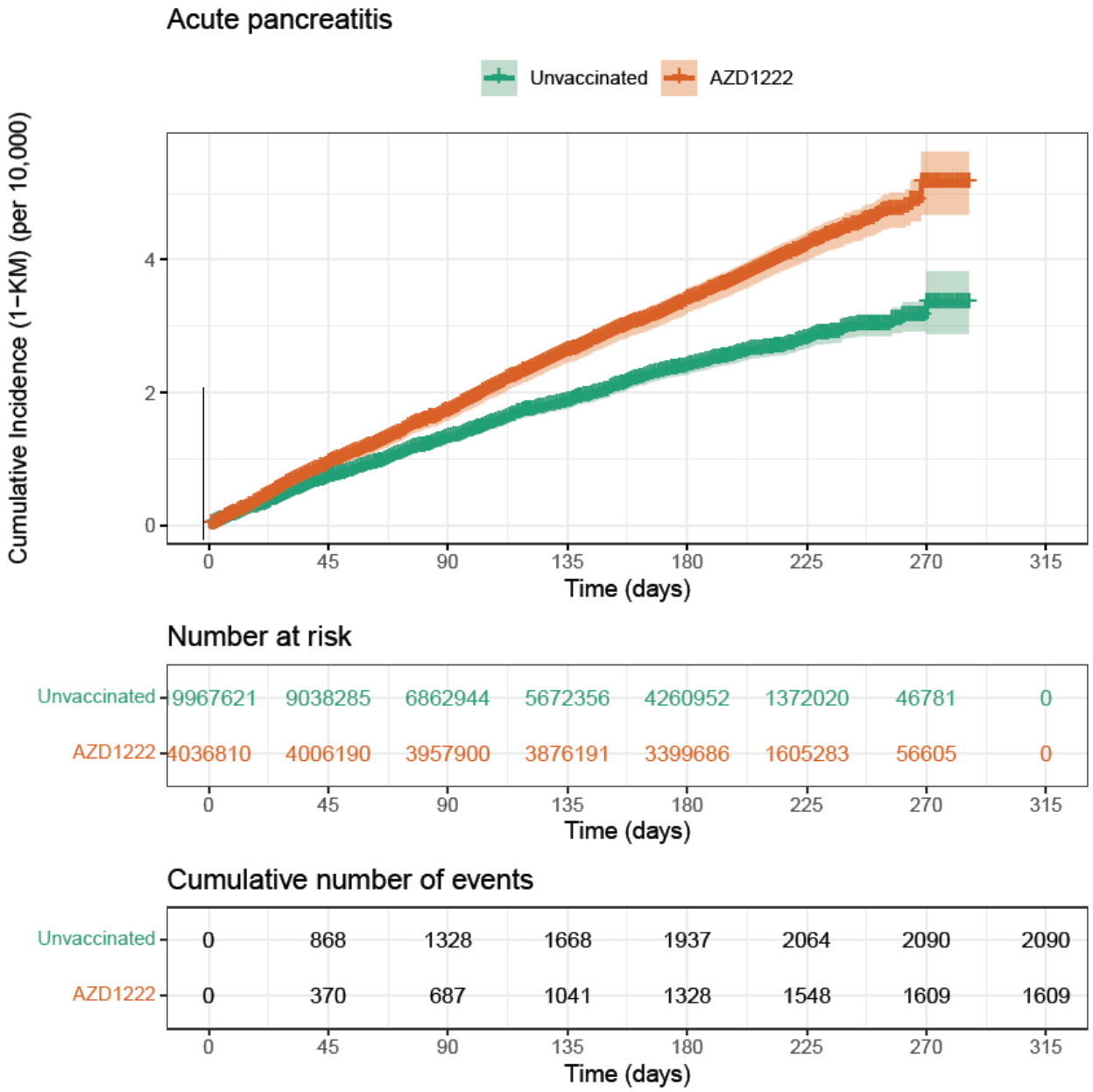


Figure 5.CPRD. Multiple Sclerosis and Other Demyelinating Disorders, Cumulative Incidence With Unknown Risk Window

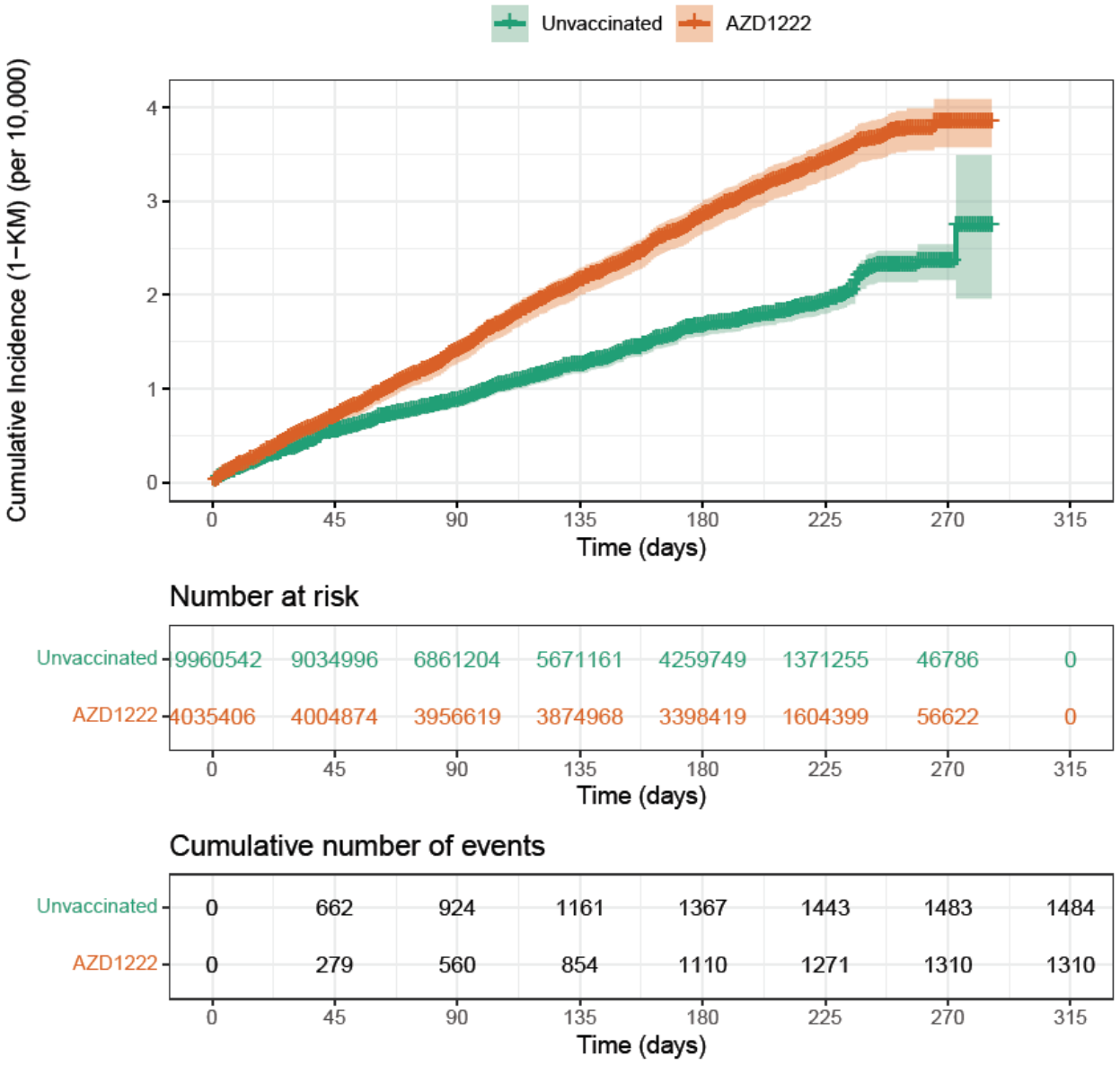


Figure 5.CPRD. Fibromyalgia, Cumulative Incidence With Unknown Risk Window

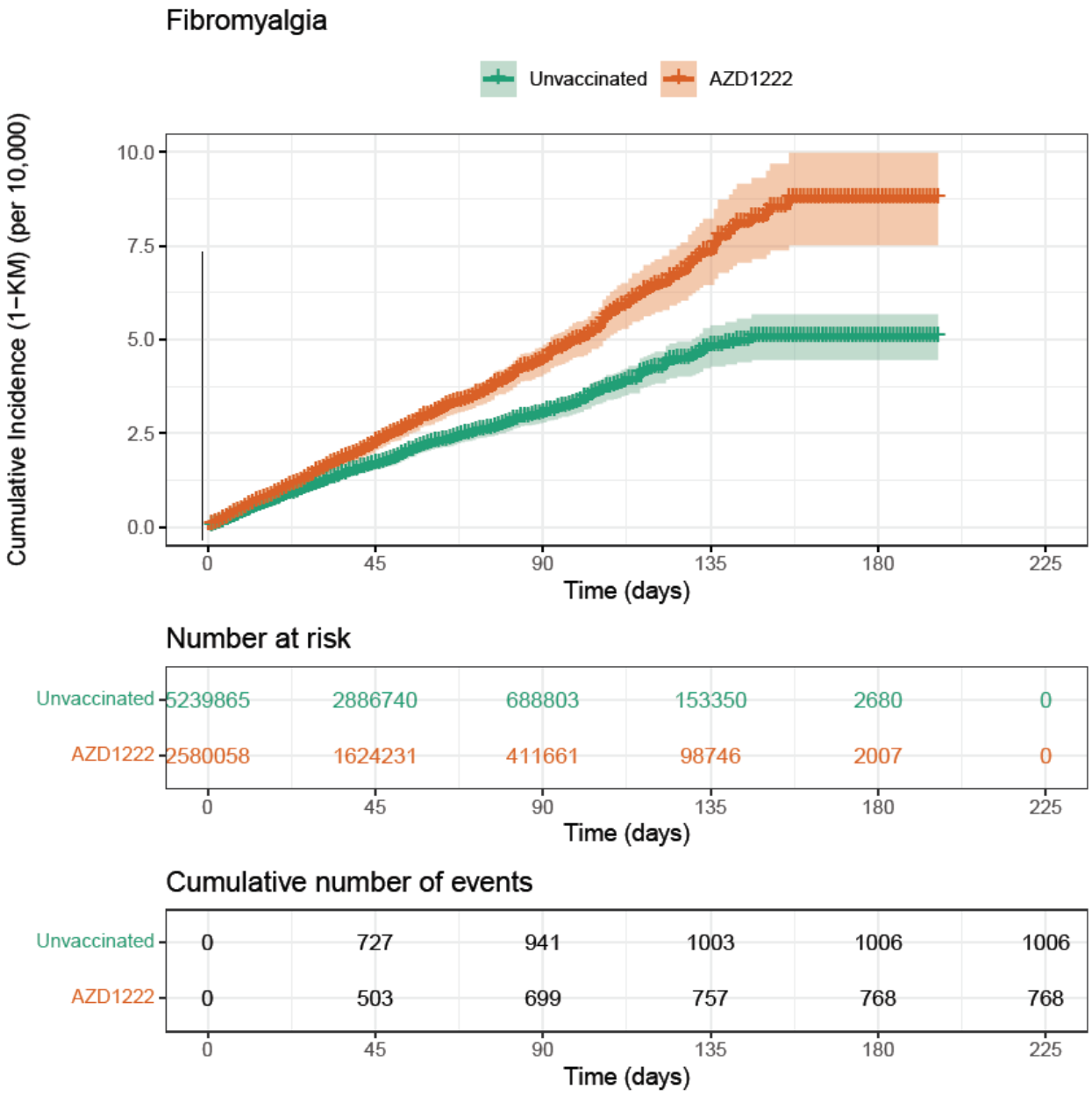


Figure 5.CPRD. Chronic Fatigue Syndrome/ME/PVFS, Cumulative Incidence With Unknown Risk Window

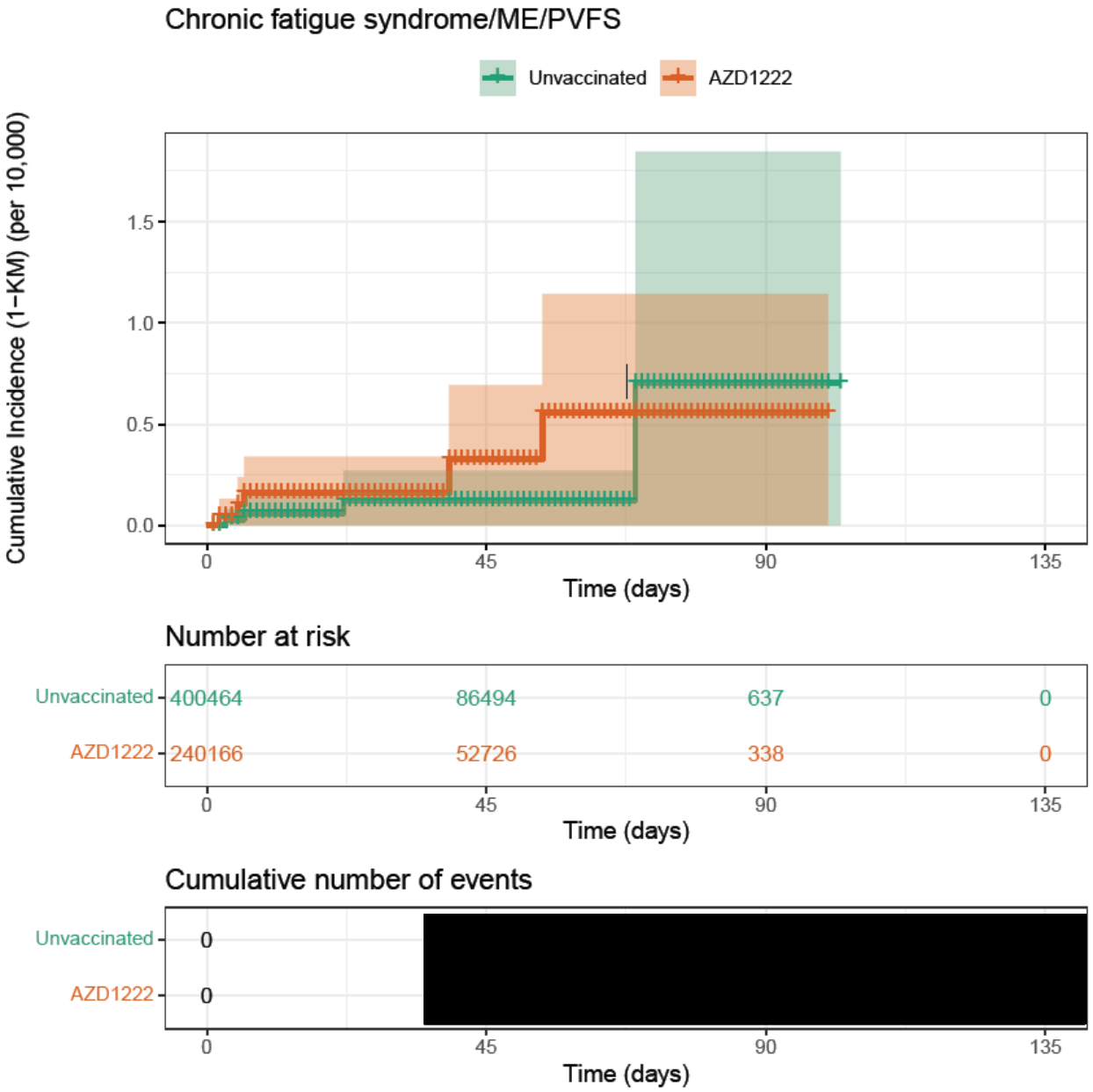


Figure 5.CPRD. Anosmia, Ageusia, Cumulative Incidence With Unknown Risk Window

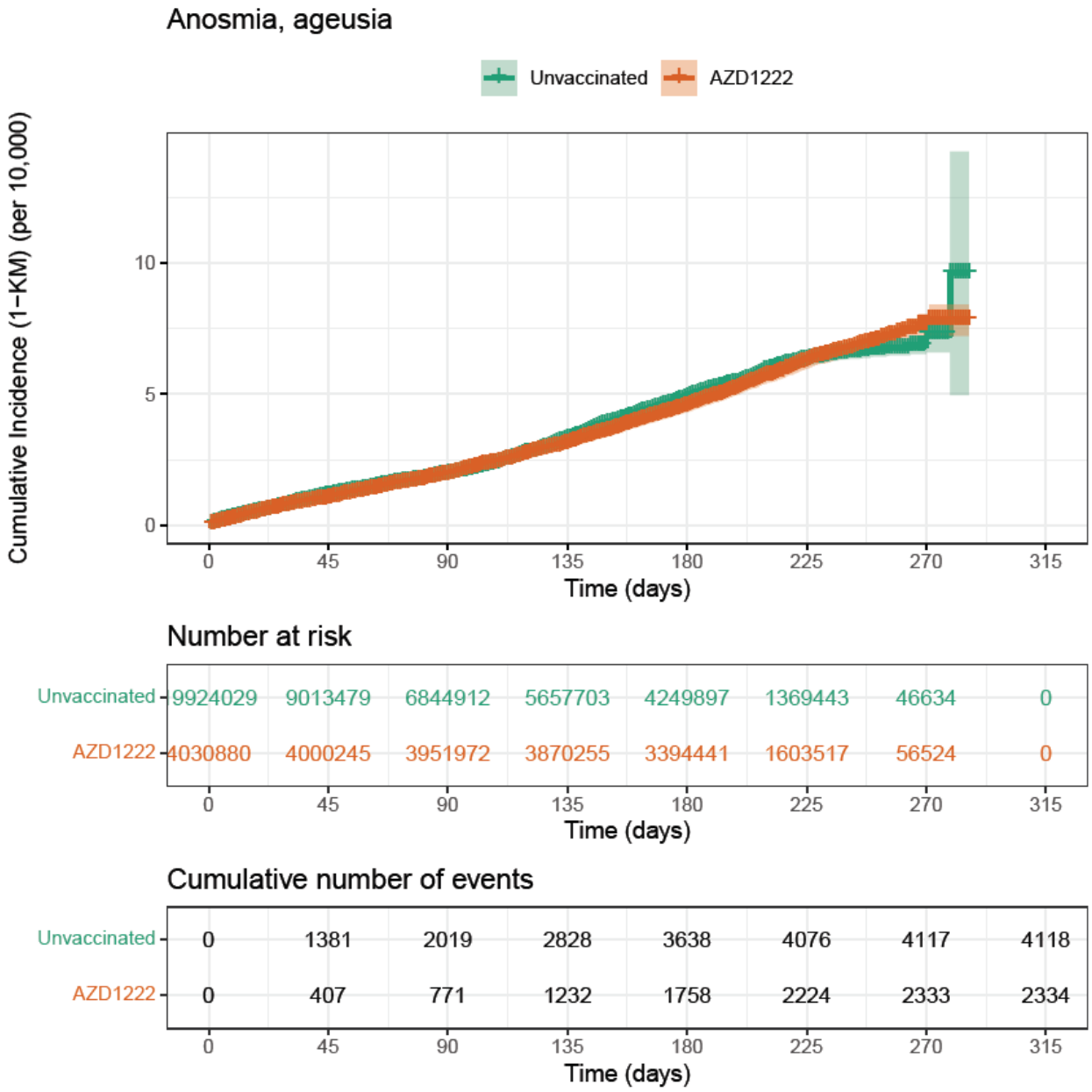


Figure 5.CPRD. Type III Hypersensitivity Reactions, Cumulative Incidence With Unknown Risk Window

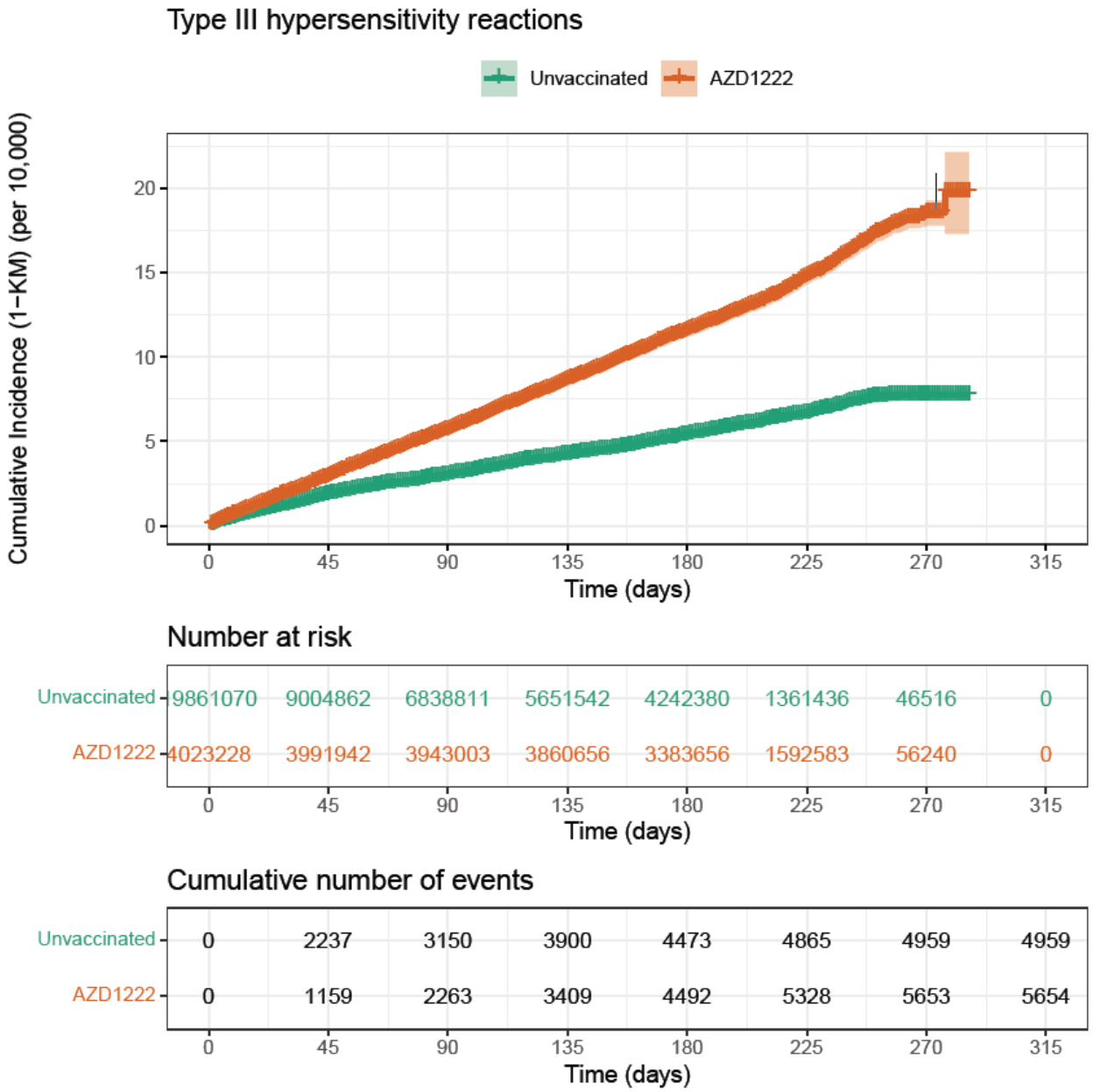


Figure 5.CPRD. Erythema Multiforme, Cumulative Incidence With Unknown Risk Window

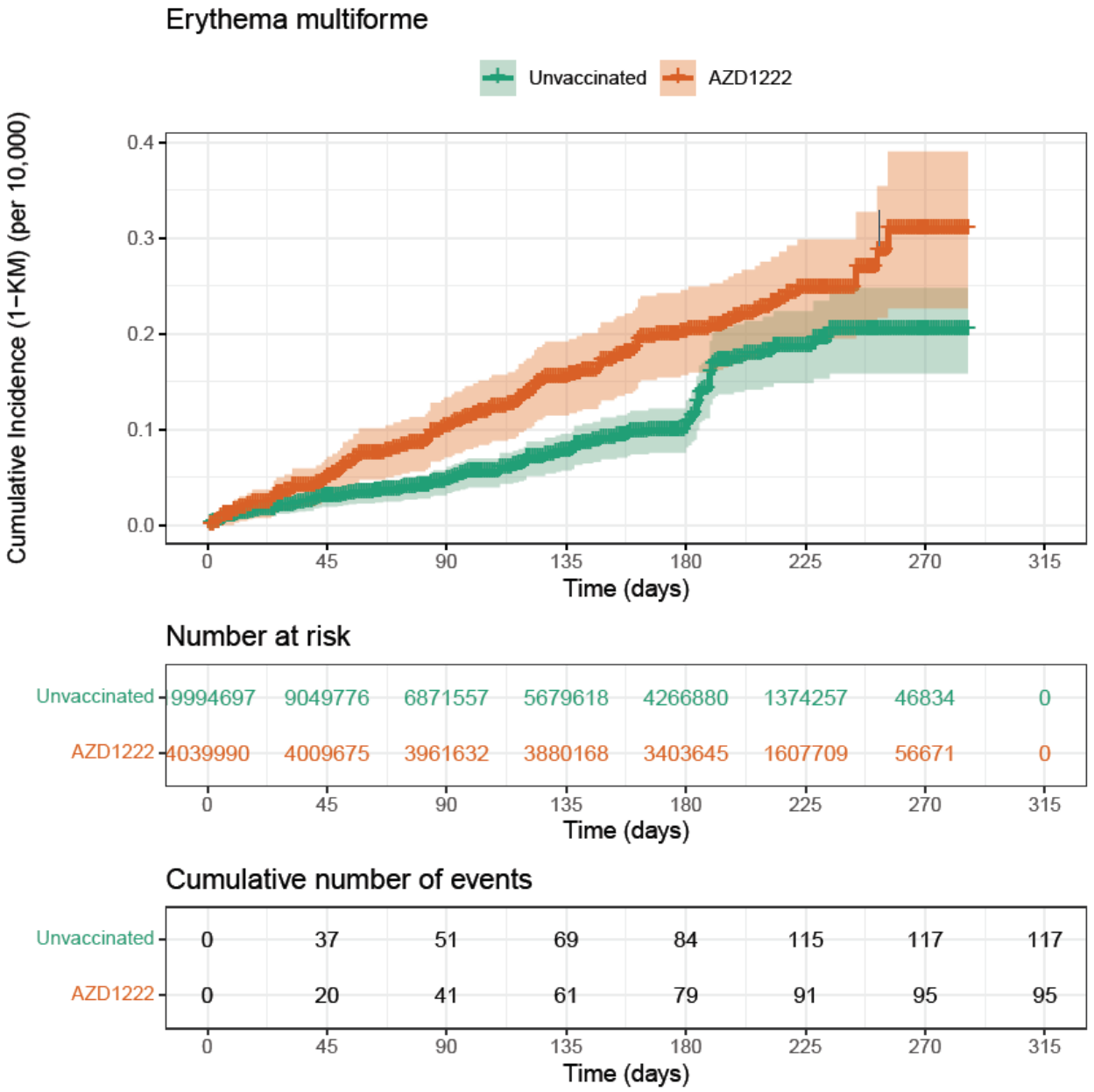
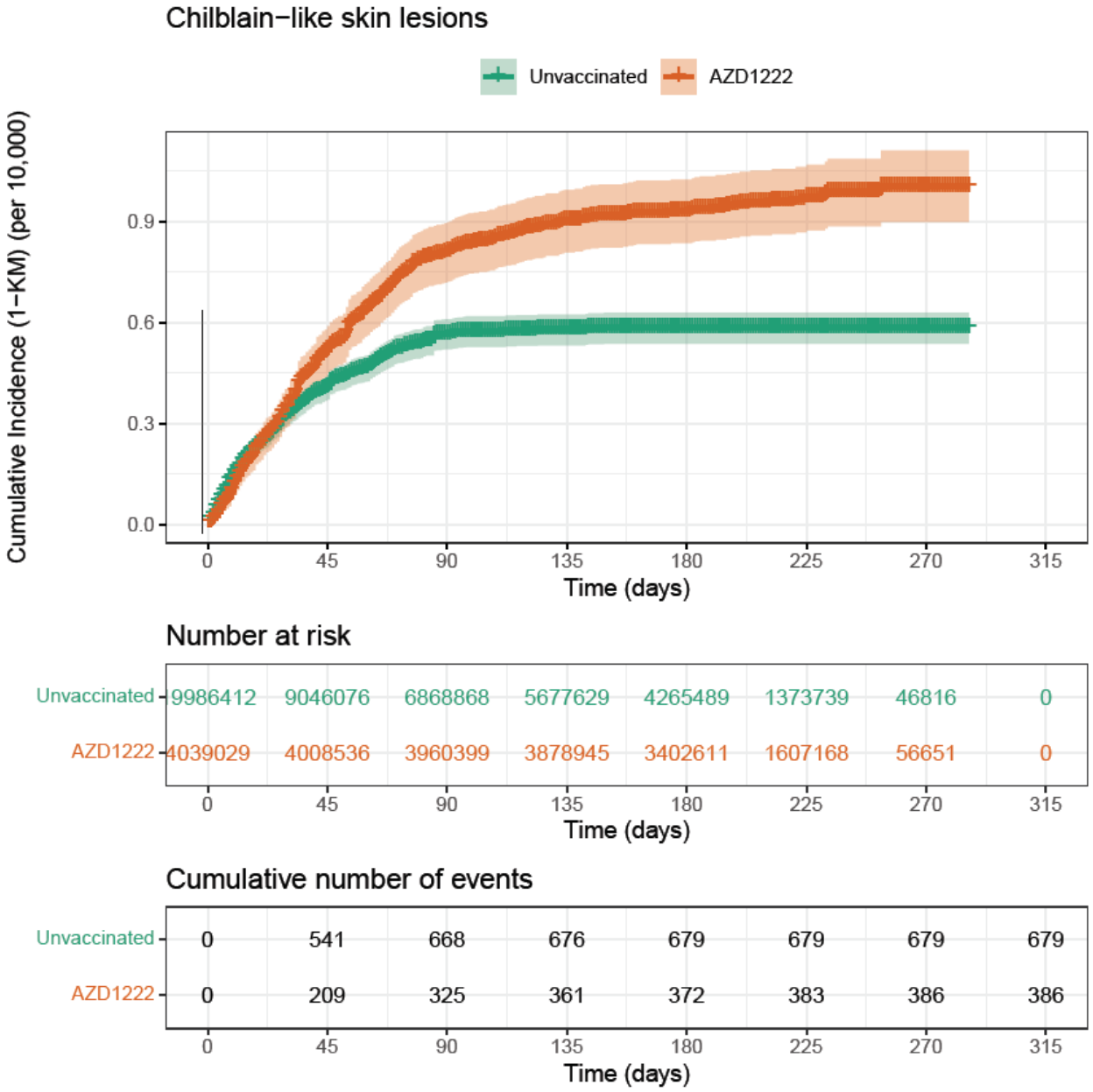


Figure 5.CPRD. Chilblain-Like Skin Lesions, Cumulative Incidence With Unknown Risk Window



B 2.2 SIDIAP, Catalonia, Spain

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Figure 5.SIDIAP. Multiple Sclerosis and Other Demyelinating Disorders, Cumulative Incidence With Unknown Risk Window

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Figure 5.SIDIAP. Chilblain-Like Skin Lesions, Cumulative Incidence With Unknown Risk Window

Table 1.1.SIDIAP. Baseline Characteristics Among the *All Vaccinated Population*, AZD1222 Cohort

	Over all the study period included in interim report 1	
	N	%[a]
Total	560,744	100.00%
Calendar quarter at index date		
Q1 2021	216,443	38.60%
Q2 2021	344,301	61.40%
Q3 2021	0	0.00%
Q4 2021	0	0.00%
Q1 2022	0	0.00%
Q2 2022	0	0.00%
Duration of lookback period (years)		
Mean (SD)	14.75	(2.21)
Median (Q1, Q3)	15	(15,15)
Age at index date (years)		
Mean (SD)	57.75	(11.67)
Median (Q1, Q3)	62	(59,65)
Age groups (years)		
0-11	[redacted]	
12-15	0	0.00%
16-19	1,967	0.35%
20-29	24,973	4.45%
30-39	34,327	6.12%
40-49	49,273	8.79%
50-59	59,609	10.63%
60-69	390,465	69.63%
70-79	125	0.02%
80+	[redacted]	
Sex, female	305,913	54.55%
COVID-19 history (diagnosis or test)	35,683	6.36%

N, number; Q1, quartile 1; Q3, quartile 3; SD, standard deviation.
[a] Counts and percentages, unless otherwise specified.

Table 2.1.SIDIAP. Incidence Rates or Prevalence Proportions of AESIs With Well-Defined Risk Window and Cumulative Incidence (1 − KM) of AESIs With Unknown Risk Window Among the *All Vaccinated Population*

		All AZD1222 vaccinated population				
AESI (risk window, days)	Risk esti-mator	N Subjects	N Out-comes	Person-years	Risk per 10,000	95% CI
Myasthenia gravis[a] (1-365)	1-KM	559,431	11	129,291.8	0.29	(0.00-14.06)
Thrombosis without thrombocytopenia[b] (1-42)	IR	559,441	[redacted]	[redacted]	0.13	(0.00-0.74)
Thrombosis with thrombocytopenia syndrome[b] (1-42)	IR	559,441	5	75,001.6	0.67	(0.22-1.56)
Narcolepsy[b] (1-42)	IR	559,453	[redacted]	[redacted]	0.27	(0.03-0.96)
Thrombocytopenia with associated bleeding[b] (1-42)	IR	559,438	5	75,001.3	0.67	(0.22-1.56)
Autoimmune thyroiditis[a] (1-180)	1-KM	559,218	74	129,233.5	2.14	(0.00-15.92)
Acute aseptic arthritis[b] (1-42)	IR	557,200	378	74,697.1	50.60	(45.63-55.97)
Guillain-Barré syndrome[b] (1-42)	IR	559,443	9	75,001.9	1.20	(0.55-2.28)
Thrombocytopenia[b] (1-42)	IR	558,805	118	74,912.6	15.75	(13.04-18.86)
Capillary leak syndrome[a] (1-365)	1-KM	NA				
Postural orthostatic tachycardia syndrome[b] (1-42)	IR	NA				
Acute cardiac injury including microangiopathy, cardiogenic shock, heart failure[b] (1-90)	IR	557,788	312	125,052.5	24.95	(22.26-27.88)
Stress cardiomyopathy[b] (1-42)	IR	559,434	6	75,000.9	0.80	(0.29-1.74)
Myocardial infarction[b] (1-28)	IR	558,382	100	53,478.3	18.70	(15.21-22.74)
Myocarditis/Pericarditis[b] (1-42)	IR	559,309	18	74,983.7	2.40	(1.42-3.79)
Acute pancreatitis[a] (1-365)	1-KM	559,026	79	129,201.3	1.80	(0.00-15.57)
Acute kidney injury[b] (1-14)	IR	558,084	70	28,876.7	24.24	(18.90-30.63)
Acute liver injury[b] (1-14)	IR	559,223	7	28,931.2	2.42	(0.97-4.99)
Multiple sclerosis, and other demyelinating disorders[a] (1-365)	1-KM	559,354	19	129,272.6	0.70	(0.00-14.47)
Transverse myelitis[b] (1-90)	IR	559,457	0	125,402.3	0.00	(0.00-0.29)
Encephalitis (including ADEM)[b] (1-42)	IR	559,439	6	75,001.2	0.80	(0.29-1.74)

AESI (risk window, days)	Risk esti-mator	All AZD1222 vaccinated population				
		N Subjects	N Out-comes	Person-years	Risk per 10,000	95% CI
Other peripheral and polyneuropathies[b] (1-42)	IR	558,903	78	74,929.3	10.41	(8.23-12.99)
Generalised convulsions[b] (0-14)	IR	560,130	32	31,250.5	10.24	(7.00-14.46)
Optic neuritis/neuromyelitis optica spectrum disorder[b] (1-42)	IR	559,408	9	74,997.7	1.20	(0.55-2.28)
Bell's palsy[b] (1-42)	IR	558,921	74	74,930.8	9.88	(7.75-12.40)
Fibromyalgia[a] (91-365)	1-KM	102,201	70	8,603.3	9.01	(0.00-40.24)
Chronic fatigue syndrome/ME/PVFS[a] (183-365)	1-KM	0[d]				
Anosmia, ageusia[a] (1-365)	1-KM	559,141	59	129,216.9	2.11	(0.00-15.92)
Type III hypersensitivity reactions[a] (1-365)	1-KM	558,860	131	129,149.0	2.93	(0.00-16.71)
Anaphylaxis[c] (0-2)	PP	560,653	6	6,910.1	0.11	(0.04-0.23)
Rhabdomyolysis[b] (1-42)	IR	559,405	6	74,997.5	0.80	(0.29-1.74)
Multisystem inflammatory syndrome in adults/children[b] (1-42)	IR	559,454	[redacted]	[redacted]	0.27	(0.03-0.96)
Sudden death[c] (0-6)	PP	560,688	0	15,654.5	0.00	(0.00-0.07)
Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease, including ARDS[a] (14-365)	1-KM	557,803	32	108,652.4	0.70	(0.00-18.89)
ARDS[b] (1-28)	IR	559,226	22	53,556.7	4.11	(2.57-6.22)
Erythema multiforme[a] (1-365)	1-KM	559,438	8	129,293.2	0.17	(0.00-13.94)
Chilblain-like skin lesions[a] (1-365)	1-KM	559,255	17	129,244.4	0.44	(0.00-14.21)

ADEM, acute disseminated encephalomyelitis; AESI, adverse event of special interest; ARDS, acute respiratory distress syndrome; CI, confidence interval; IR, incidence rate; KM, Kaplan-Meier; ME, myalgic encephalitis; N, number; NA, not available; PR, prevalence rate; PVFS, postviral fatigue syndrome; PY, person-years.

[a] Cumulative incidence (1-KM) per 10,000, for these outcomes with unknown risk windows.

[b] Incidence rate (IR) per 10,000 person-years, for outcomes with well-defined risk windows.

[c] Prevalence proportion (PP) per 10,000, for outcomes with well-defined and very short risk windows.

[d] For chronic fatigue syndrome, 0 subjects means that this AESI could not be evaluated because less than 6 months of follow-up was included in the interim 1 report.

Table 2.SIDIAP. TTS. Cumulative Incidence (1 − KM) of Thrombosis With Thrombocytopenia Syndrome Among the *All Vaccinated Population*, by Age Groups and Sex

	All AZD1222 vaccinated population				
	N Subjects	N Out-comes	Person-years	1-KM per 10,000	95% CI
By age groups (years)					
0-11	[redacted]	[redacted]	[redacted]	0.00	(0.00-5245.32)
12-15	0				
16-19	1,963	0	314.3	0.00	(0.00-306.53)
20-29	24,895	0	4,202.1	0.00	(0.00-82.09)
30-39	34,148	0	5,851.2	0.00	(0.00-70.10)
40-49	48,980	[redacted]	[redacted]	0.41	(0.00-61.11)
50-59	59,434	[redacted]	[redacted]	0.17	(0.00-55.65)
60-69	389,894	[redacted]	[redacted]	0.05	(0.00-21.80)
70-79	122	0	11.0	0.00	(0.00-1202.22)
80+	[redacted]	[redacted]	[redacted]	0.00	(0.00-4588.78)
By sex					
Male	254,276	[redacted]	[redacted]	0.12	(0.00-27.05)
Female	305,165	[redacted]	[redacted]	0.07	(0.00-24.64)

CI, confidence interval; KM, Kaplan-Meier; N, number; PY, person-years.
[a] Numbers correspond to counts and percentages unless otherwise specified.

Table 3.1.SIDIAP. Description of the Utilisation Pattern of Subsequent Doses of a COVID-19 Vaccine in the *All Vaccinated First Dose Population*, Over All the Study Period

AZD1222 cohort	Over all the study period included in interim report 1[a]	
	N	%
Subjects with a first dose of AZD1222 (Vaxzevria)	560,712	
Subjects who had received only a first dose of AZD1222 at the end of study period for interim report 1	255,402	45.55%
Subjects with a first dose of AZD122 who receive a second dose of any COVID-19 vaccine and time between doses	305,310	54.45%
Vaxzevria (COVID-19 Vaccine AstraZeneca)	293,335	52.31%
Time between dose 1 and dose 2, weeks		
Mean (SD)	12.30	(1.54)
Median (Q1-Q3)	12.0	(11.3,13.1)
min, max	2,	20
<2 weeks	0	0.00%
2-4 weeks	108	0.04%
5-8 weeks	475	0.16%
9-12 weeks	211,852	72.22%
13-18 weeks	80,850	27.56%
>18 weeks	50	0.02%
Comirnaty (COVID-19 Vaccine Pfizer-BioNTech)	11,962	2.13%
Time between dose 1 and dose 2, weeks		
Mean (SD)	13.59	(2.06)
Median (Q1-Q3)	13.9	(12.4,14.9)
min, max	3,	20
<2 weeks	0	0.00%
2-4 weeks	175	1.46%
5-8 weeks	78	0.65%
9-12 weeks	3,615	30.22%
13-18 weeks	8,074	67.50%
>18 weeks	20	0.17%

AZD1222 cohort	Over all the study period included in interim report 1[a]	
	N	%
Spikevax (COVID-19 Vaccine Moderna)	12	<0.01%
Time between dose 1 and dose 2, weeks		
Mean (SD)	7.31	(3.93)
Median (Q1-Q3)	5.7	(4.3,9.7)
min, max	3,	15
<2 weeks	0	0.00%
2-4 weeks	5	41.67%
5-8 weeks	[redacted]	
9-12 weeks	[redacted]	
13-18 weeks	[redacted]	
>18 weeks	0	0.00%
COVID-19 Vaccine Janssen	[redacted]	
Time between dose 1 and dose 2, weeks		
Mean (SD)	[redacted]	
Median (Q1-Q3)	[redacted]	
min, max	[redacted]	
<2 weeks	[redacted]	
2-4 weeks	0	0.00%
5-8 weeks	0	0.00%
9-12 weeks	0	0.00%
13-18 weeks	[redacted]	
>18 weeks	0	0.00%
Other COVID-19 vaccines	0	0.00%
Time between dose 1 and dose 2, weeks		
Mean (SD)		
Median (Q1-Q3)		
min, max		
<2 weeks	0	0.00%
2-4 weeks	0	0.00%
5-8 weeks	0	0.00%
9-12 weeks	0	0.00%
13-18 weeks	0	0.00%
>18 weeks	0	0.00%

AZD1222 cohort	Over all the study period included in interim report 1[a]	
	N	%
Subjects with a first and second dose of AZD122 who receive a third dose of any COVID-19 vaccine and time between doses	[redacted]	
Vaxzevria (COVID-19 Vaccine AstraZeneca)	[redacted]	
Time between dose 2 and dose 3		
Mean (SD)	7.00	(0.61)
Median (Q1-Q3)	7.0	(6.8,7.2)
min, max	7,	7
<12 weeks	[redacted]	
12-24 weeks	[redacted]	
25-37 weeks	0	0.00%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%
Comirnaty (COVID-19 Vaccine Pfizer-BioNTech)	0	0.00%
Time between dose 2 and dose 3		
Mean (SD)		
Median (Q1-Q3)		
min, max		
<12 weeks	0	0.00%
12-24 weeks	0	0.00%
25-37 weeks	0	0.00%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%
Spikevax (COVID-19 Vaccine Moderna)	0	0.00%
Time between dose 2 and dose 3		
Mean (SD)		
Median (Q1-Q3)		
min, max		
<12 weeks	0	0.00%
12-24 weeks	0	0.00%
25-37 weeks	0	0.00%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%

AZD1222 cohort	Over all the study period included in interim report 1[a]	
	N	%
COVID-19 Vaccine Janssen	0	0.00%
Time between dose 2 and dose 3		
Mean (SD)		
Median (Q1-Q3)		
min, max		
<12 weeks	0	0.00%
12-24 weeks	0	0.00%
25-37 weeks	0	0.00%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%
Other COVID-19 vaccines	0	0.00%
Time between dose 2 and dose 3		
Mean (SD)		
Median (Q1-Q3)		
min, max		
<12 weeks	0	0.00%
12-24 weeks	0	0.00%
25-37 weeks	0	0.00%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%

Q1 = Quartile 1; Q3 = Quartile 3; SD = Standard deviation.

Table 4.SIDIAP. Cohort Attrition for the *Matched Population*

Cohort	N	(%)
AZD1222 cohort		
All vaccinated population	560,744	
All vaccinated first dose population	560,712	(99.99%)
And with at least 12 months lookback period (eligible to be matched)	558,568	(99.62%)
Unique vaccinated subjects not matched	[redacted]	
Unique vaccinated subjects matched	558,566	(100.00%)
Matching ratio 1:1	[redacted]	
Matching ratio 1:2	[redacted]	
Matching ratio 1:3	0	(0.00%)
Matching ratio 1:4	0	(0.00%)
Matching ratio 1:5	558,564	(100.00%)
Unvaccinated cohort		
Unique subjects with no record of vaccination with any COVID-19 vaccine during the study period	5,419,960	
And with at least 12 months lookback period (eligible to be matched)	5,308,949	(97.95%)
Unique unvaccinated subjects matched	1,128,799	(21.26%)
Unique unvaccinated subjects not matched	4,180,150	(78.74%)
Non-unique unvaccinated subjects matched	2,792,824	
Number of times an unvaccinated subject was matched		
Median (Q1-Q3)	1	(1-3)
Min-Max		1-22
1	629,657	(55.78%)
2	174,798	(15.49%)
3	85,332	(7.56%)
4	59,612	(5.28%)
5 or more	179,400	(15.89%)

N = number; Q1 = Quartile 1; Q3 = Quartile 3.

Table 5.SIDIAP. Reasons for Censoring Follow-up Among the *Matched Population* Cohorts

	AZD1222 cohort		Unvaccinated cohort	
Cohort design	**N**	**(%)**	**N**	**(%)**
Total	558,566	(100.00%)	2,792,824	(100.00%)
Person-months of follow-up				
Mean follow-up (SD), months	2.75	(0.86)	1.71	(1.36)
Median follow-up (Q1-Q3), months	2.8	(2.1-3.2)	1.4	(0.4-2.8)
P1 - P99 follow-up, months	0.9	-4.6	<0.1	-4.6
Received AZD1222, n (%)	0	(0.00%)	1,092,397	(39.11%)
Received any COVID-19 vaccine other than AZD1222, n (%)	11,886	(2.13%)	750,896	(26.89%)
Censored 365 days after the second dose of AZD1222, n (%)	0	(0.00%)	0	(0.00%)
End of study period, n (%)	544,674	(97.51%)	935,844	(33.51%)
Enrolment termination date in the health plan or system, n(%)	1,831	(0.33%)	9,813	(0.35%)
Death, n(%)	175	(0.03%)	3,874	(0.14%)

N = number; Q1 = Quartile 1; Q3 = Quartile 3.

Table 11.1.SIDIAP. Crude Risk Estimates for AESIs in the *Matched Cohorts* Based on Definition and Duration of Risk Windows

		AZD1222 cohort					Unvaccinated cohort				
AESI (risk window, days)	**Risk esti-mator**	**N Patients**	**N Out-comes**	**Person-years**	**Risk per 10,000**	**95% CI**	**N Patients**	**N Out-comes**	**Person-years**	**Risk per 10,000**	**95% CI**
Myasthenia gravis[a] (1-365)	1-KM	557,332	11	128,845.9	0.29	(0.00-14.49)	2,786,087	21	397,368.7	0.16	(0.00-6.33)
Thrombosis without thrombocytopenia[b] (1-42)	IR	557,342	[redacted]	[redacted]	0.13	(0.00-0.75)	2,786,302	[redacted]	[redacted]	0.08	(0.02-0.32)
Thrombosis with thrombocytopenia syndrome[b] (1-42)	IR	557,342	5	74,736.9	0.67	(0.22-1.56)	2,786,270	5	252,218.9	0.20	(0.05-0.73)
Narcolepsy[b] (1-42)	IR	557,354	[redacted]	[redacted]	0.27	(0.03-0.97)	2,786,435	7	252,230.4	0.28	(0.08-1.00)
Thrombocytopenia with associated bleeding[b] (1-42)	IR	557,339	5	74,736.7	0.67	(0.22-1.56)	2,786,281	7	252,218.1	0.28	(0.10-0.76)
Autoimmune thyroiditis[a] (1-180)	1-KM	557,120	74	128,788.0	2.15	(0.00-16.35)	2,784,080	238	397,043.6	2.09	(0.00-8.27)
Acute aseptic arthritis[b] (1-42)	IR	555,109	374	74,433.8	50.25	(45.28-55.61)	2,764,935	915	250,618.3	36.51	(32.07-41.56)
Guillain-Barré syndrome[b] (1-42)	IR	557,344	9	74,737.3	1.20	(0.55-2.29)	2,786,300	20	252,219.5	0.79	(0.28-2.24)
Thrombocytopenia[b] (1-42)	IR	556,708	118	74,648.3	15.81	(13.08-18.93)	2,779,287	558	251,627.6	22.18	(18.52-26.55)
Capillary leak syndrome[a] (1-365)	1-KM	NA					NA				
Postural orthostatic tachycardia syndrome[b] (1-42)	IR	NA					NA				

AESI (risk window, days)	Risk esti-mator	AZD1222 cohort					Unvaccinated cohort				
		N Patients	N Out-comes	Person-years	Risk per 10,000	95% CI	N Patients	N Out-comes	Person-years	Risk per 10,000	95% CI
Acute cardiac injury including microangiopathy, cardiogenic shock, heart failure[b] (1-90)	IR	555,695	312	124,623.7	25.04	(22.33-27.97)	2,767,440	1,165	378,036.1	30.82	(26.90-35.31)
Stress cardiomyopathy[b] (1-42)	IR	557,335	6	74,736.3	0.80	(0.29-1.75)	2,786,217	[redacted]	[redacted]	0.16	(0.03-0.75)
Myocardial infarction[b] (1-28)	IR	556,288	100	53,289.8	18.77	(15.27-22.82)	2,775,223	449	190,776.9	23.54	(19.86-27.89)
Myocarditis/Pericarditis[b] (1-42)	IR	557,211	18	74,719.2	2.41	(1.43-3.81)	2,785,020	73	252,113.1	2.90	(1.86-4.51)
Acute pancreatitis[a] (1-365)	1-KM	556,928	79	128,755.7	1.80	(0.00-16.00)	2,781,917	290	396,873.3	2.11	(0.00-8.29)
Acute kidney injury[b] (1-14)	IR	555,989	70	28,776.7	24.33	(18.96-30.73)	2,769,935	411	109,675.9	37.47	(32.06-43.80)
Acute liver injury[b] (1-14)	IR	557,124	7	28,831.0	2.43	(0.98-5.00)	2,783,592	112	110,164.7	10.17	(7.61-13.58)
Multiple sclerosis, and other demyelinating disorders[a] (1-365)	1-KM	557,255	19	128,826.7	0.70	(0.00-14.89)	2,785,168	110	397,232.2	0.94	(0.00-7.11)
Transverse myelitis[b] (1-90)	IR	557,358	0	124,972.4	0.00	(0.00-0.30)	2,786,488	[redacted]	[redacted]	0.03	(0.00-0.19)
Encephalitis (including ADEM)[b] (1-42)	IR	557,340	6	74,736.6	0.80	(0.29-1.75)	2,786,256	17	252,216.8	0.67	(0.24-1.90)
Other peripheral and polyneuropathies[b] (1-42)	IR	556,805	78	74,664.8	10.45	(8.26-13.04)	2,780,695	292	251,772.9	11.60	(9.35-14.39)

AESI (risk window, days)	Risk esti-mator	AZD1222 cohort					Unvaccinated cohort				
		N Patients	N Out-comes	Person-years	Risk per 10,000	95% CI	N Patients	N Out-comes	Person-years	Risk per 10,000	95% CI
Generalised convulsions[b] (0-14)	IR	558,011	32	31,142.6	10.28	(7.03-14.51)	2,786,273	141	119,591.8	11.79	(9.23-15.05)
Optic neuritis/neuromyelitis optica spectrum disorder[b] (1-42)	IR	557,309	9	74,733.1	1.20	(0.55-2.29)	2,785,979	19	252,196.2	0.75	(0.32-1.80)
Bell's palsy[b] (1-42)	IR	556,825	74	74,666.5	9.91	(7.78-12.44)	2,780,985	300	251,776.5	11.92	(9.41-15.09)
Fibromyalgia[a] (91-365)	1-KM	97,635	68	8,490.2	8.91	(0.00-40.86)	400,429	235	31,213.3	8.92	(0.00-24.71)
Chronic fatigue syndrome/ME/PVFS[a] (183-365)	1-KM	0[d]				NR					NR
Anosmia, ageusia[a] (1-365)	1-KM	557,043	59	128,771.2	2.12	(0.00-16.35)	2,783,440	201	396,910.1	2.03	(0.00-8.22)
Type III hypersensitivity reactions[a] (1-365)	1-KM	556,765	131	128,703.8	2.94	(0.00-17.14)	2,780,139	437	396,664.4	3.31	(0.00-9.50)
Anaphylaxis[c] (0-2)	PP	558,531	6	6,886.7	0.11	(0.04-0.23)	2,792,444	7	27,752.4	0.03	(0.01-0.05)
Rhabdomyolysis[b] (1-42)	IR	557,306	6	74,732.9	0.80	(0.29-1.75)	2,785,867	35	252,182.7	1.39	(0.61-3.15)
Multisystem inflammatory syndrome in adults/children[b] (1-42)	IR	557,355	[redacted]	[redacted]	0.27	(0.03-0.97)	2,786,416	[redacted]	[redacted]	0.08	(0.02-0.32)
Sudden death[c] (0-6)	PP	558,566	0	15,601.2	0.00	(0.00-0.07)	2,792,824	0	61,792.9	0.00	(0.00-0.01)

AESI (risk window, days)	Risk esti-mator	AZD1222 cohort					Unvaccinated cohort				
		N Patients	N Out-comes	Person-years	Risk per 10,000	95% CI	N Patients	N Out-comes	Person-years	Risk per 10,000	95% CI
Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease, including ARDS[a] (14-365)	1-KM	551,100	32	107,558.0	0.71	(0.00-19.01)	2,079,271	178	308,695.0	1.25	(0.00-10.67)
ARDS[b] (1-28)	IR	557,128	22	53,367.8	4.12	(2.58-6.24)	2,783,043	199	191,202.6	10.41	(7.97-13.59)
Erythema multiforme[a] (1-365)	1-KM	557,339	8	128,847.3	0.18	(0.00-14.37)	2,786,284	29	397,379.8	0.25	(0.00-6.42)
Chilblain-like skin lesions[a] (1-365)	1-KM	557,156	17	128,798.5	0.44	(0.00-14.63)	2,784,681	91	397,099.1	0.59	(0.00-6.76)

ADEM, acute disseminated encephalomyelitis; AESI, adverse event of special interest; ARDS, acute respiratory distress syndrome; CI, confidence interval; IR, incidence rate; KM, Kaplan-Meier; ME, myalgic encephalitis; N, number; NA, not available; NR, not reportable; PR, prevalence rate; PVFS, postviral fatigue syndrome; PY, person-years.

[a] Cumulative incidence (1-KM) per 10,000, for these outcomes with unknown risk windows.

[b] Incidence rate (IR) per 10,000 person-years, for outcomes with well-defined risk windows.

[c] Prevalence proportion (PP) per 10,000, for outcomes with well-defined and very short risk windows.

[d] For chronic fatigue syndrome, 0 subjects means that this AESI could not be evaluated because less than 6 months of follow-up was included in the interim 1 report.

Figure1.SIDIAP. Number of Subjects Vaccinated With a First Dose of AZD1222 Who Were Excluded, Included, and Could Be Matched by Calendar Time

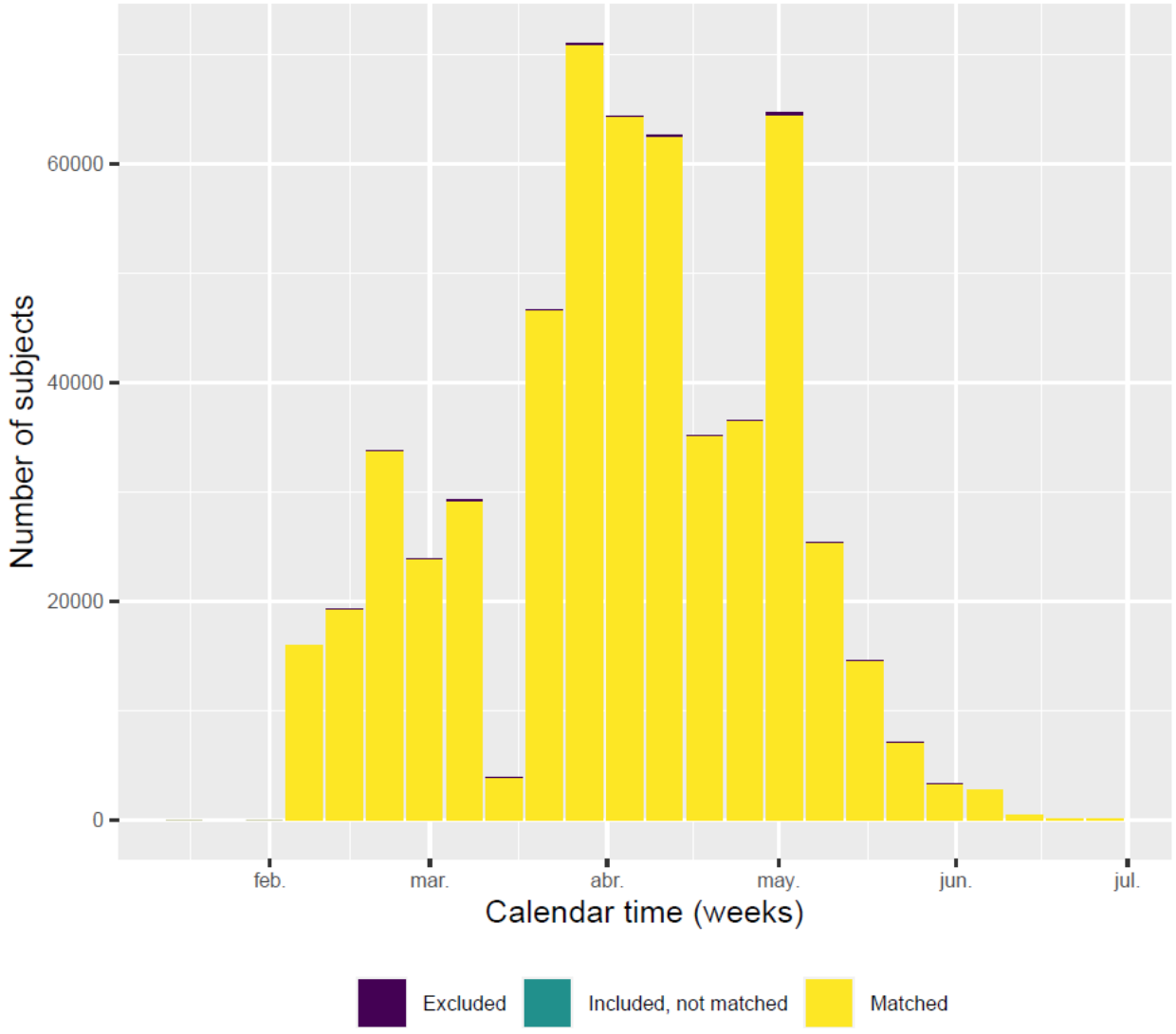

Figure2.SIDIAP. AZD1222 Cohort, Reasons for Censoring Follow-up, by Quarter

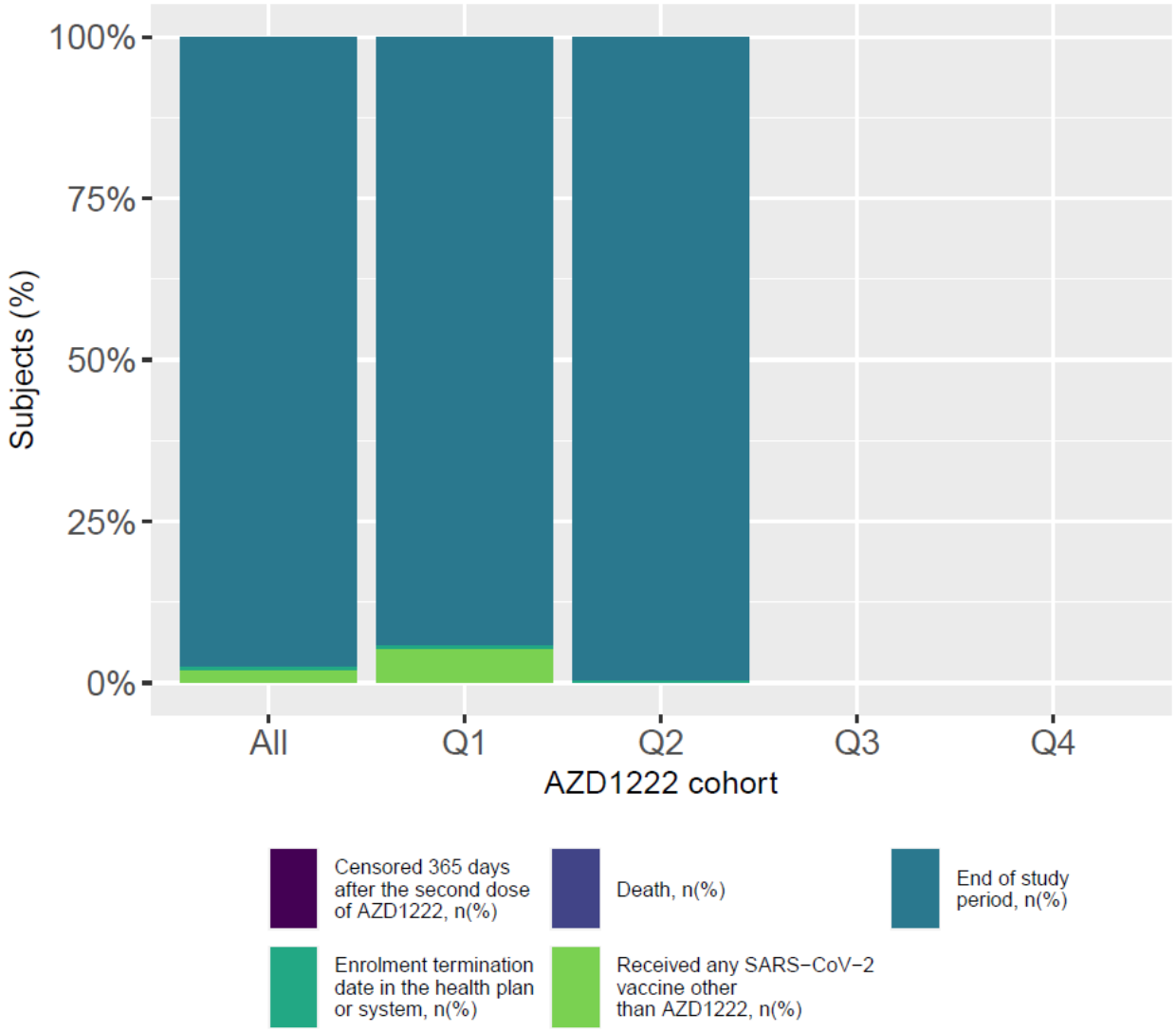

Figure2.SIDIAP. Unvaccinated Cohort, Reasons for Censoring Follow-up, by Quarter

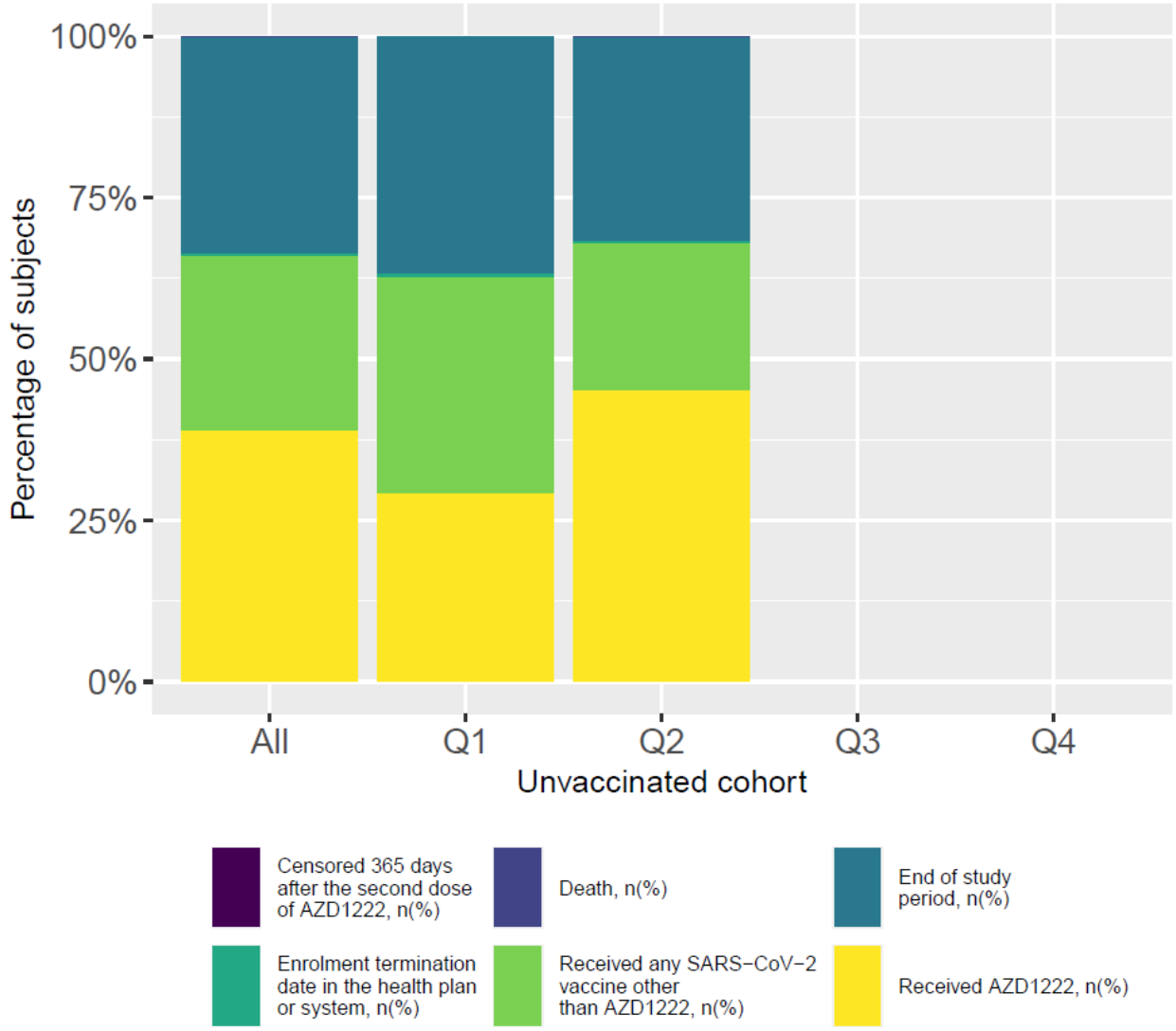

Figure 5.SIDIAP. Myasthenia Gravis, Cumulative Incidence With Unknown Risk Window

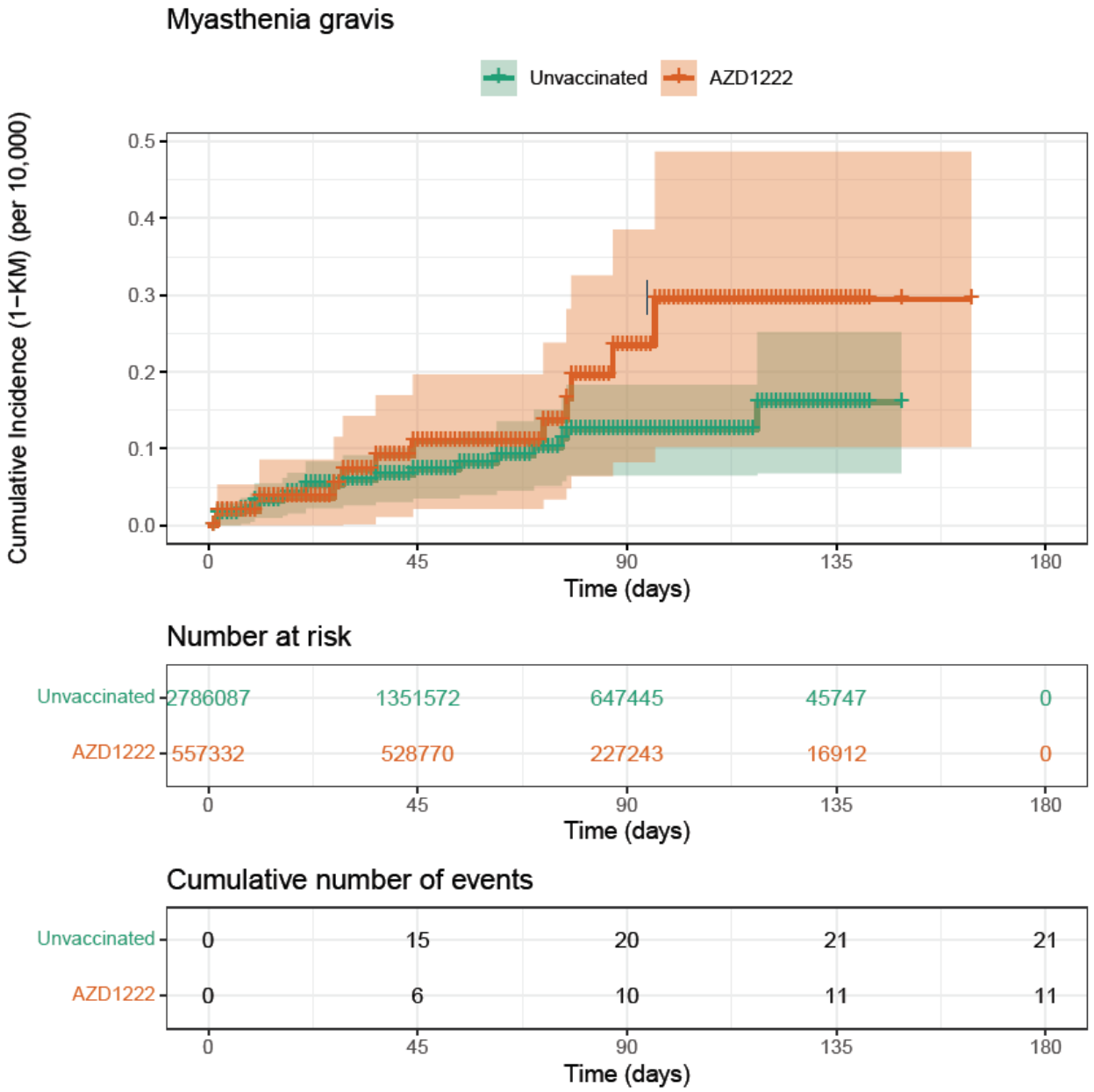

Figure 5.SIDIAP. Autoimmune Thyroiditis, Cumulative Incidence With Unknown Risk Window

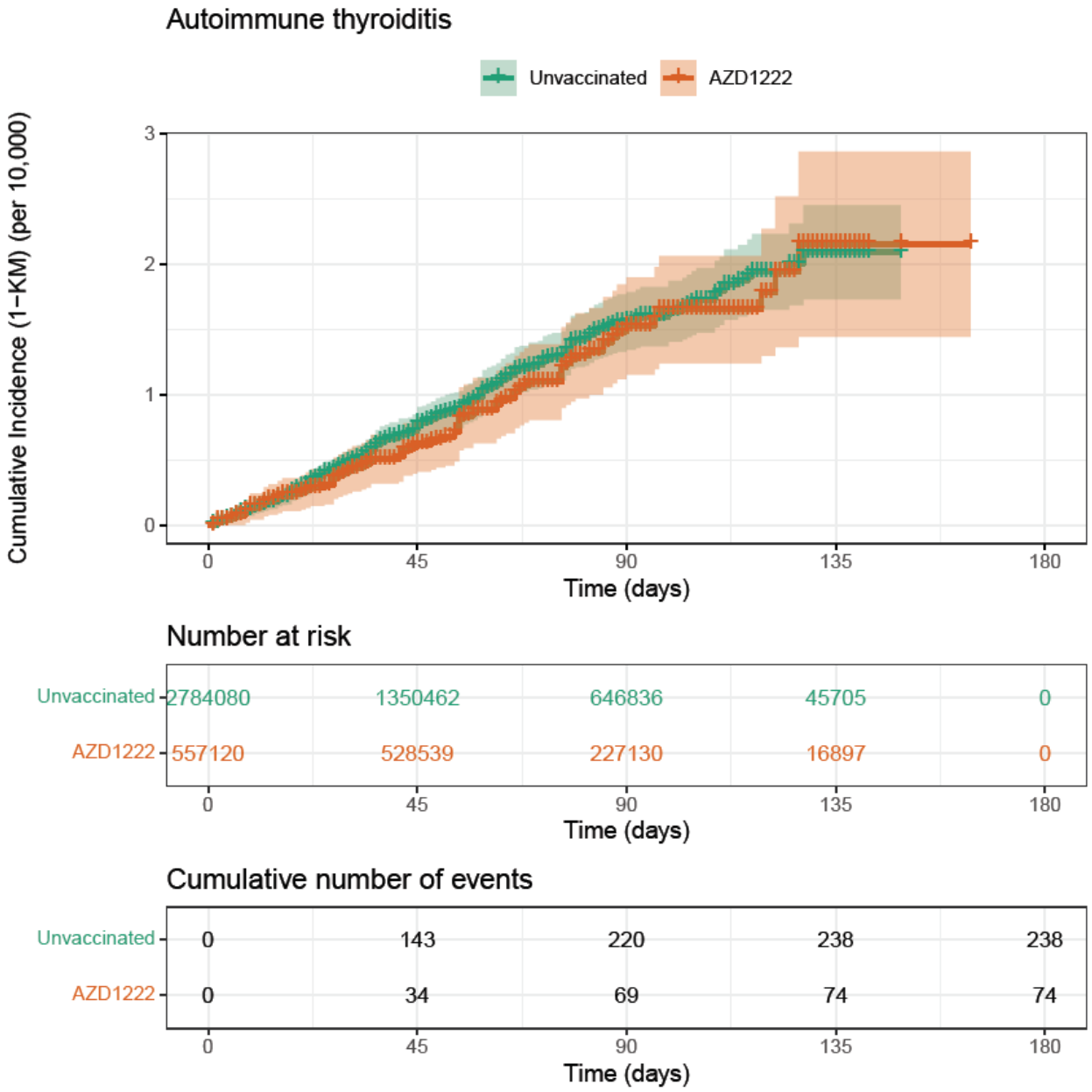

Figure 5.SIDIAP. Acute Pancreatitis, Cumulative Incidence With Unknown Risk Window

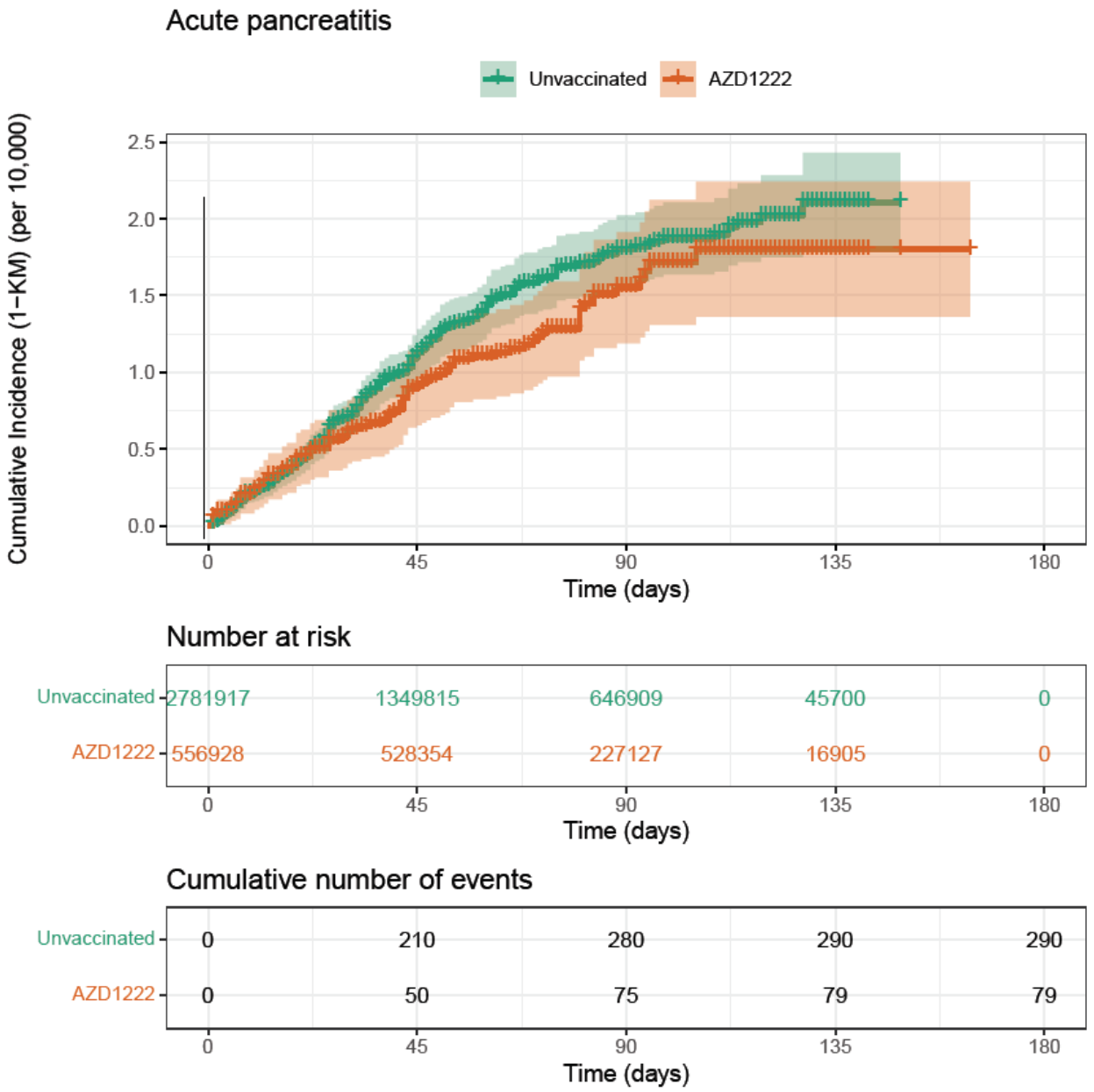

Figure 5.SIDIAP. Multiple Sclerosis and Other Demyelinating Disorders, Cumulative Incidence With Unknown Risk Window

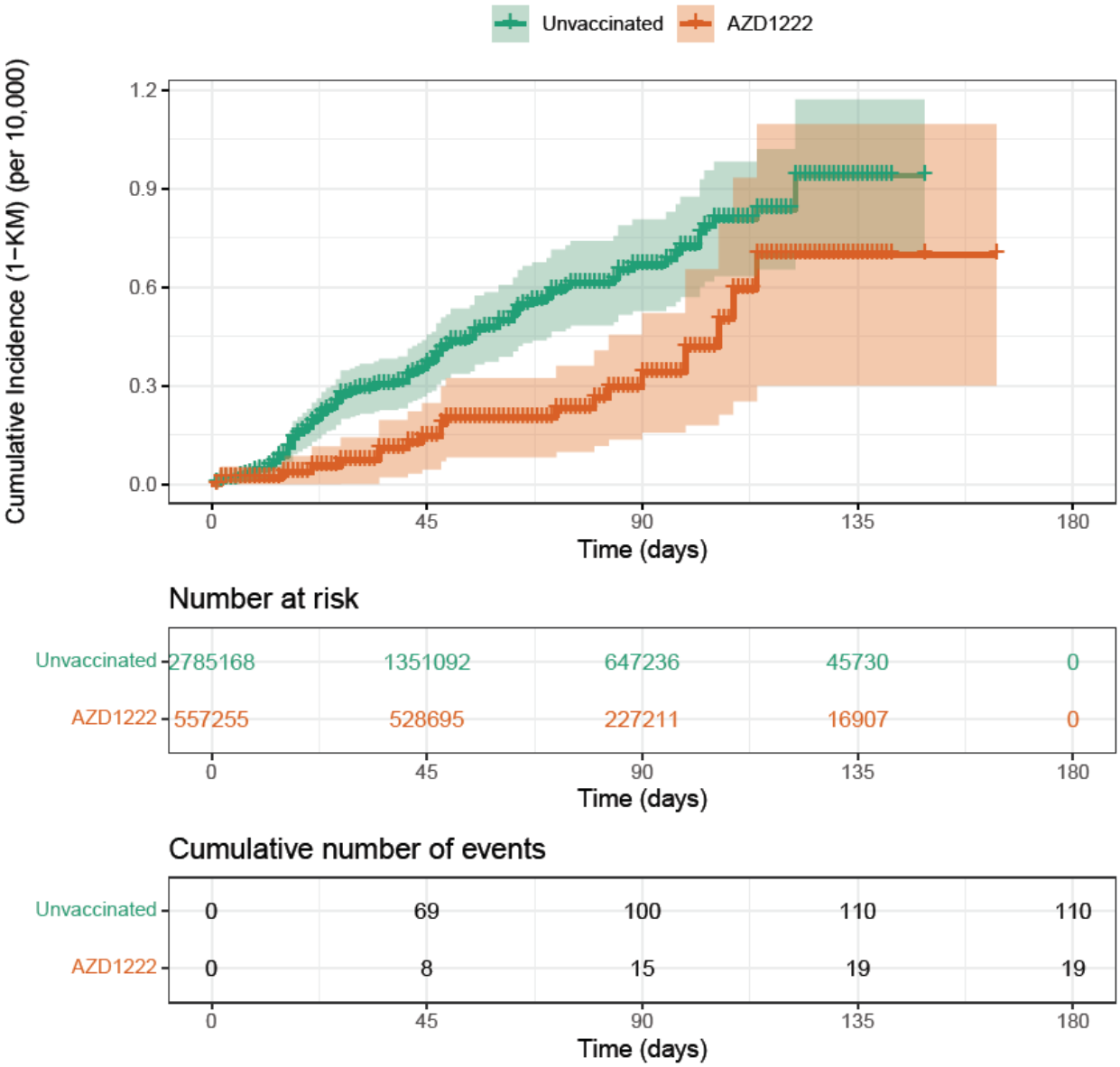

Figure 5.SIDIAP. Fibromyalgia, Cumulative Incidence With Unknown Risk Window

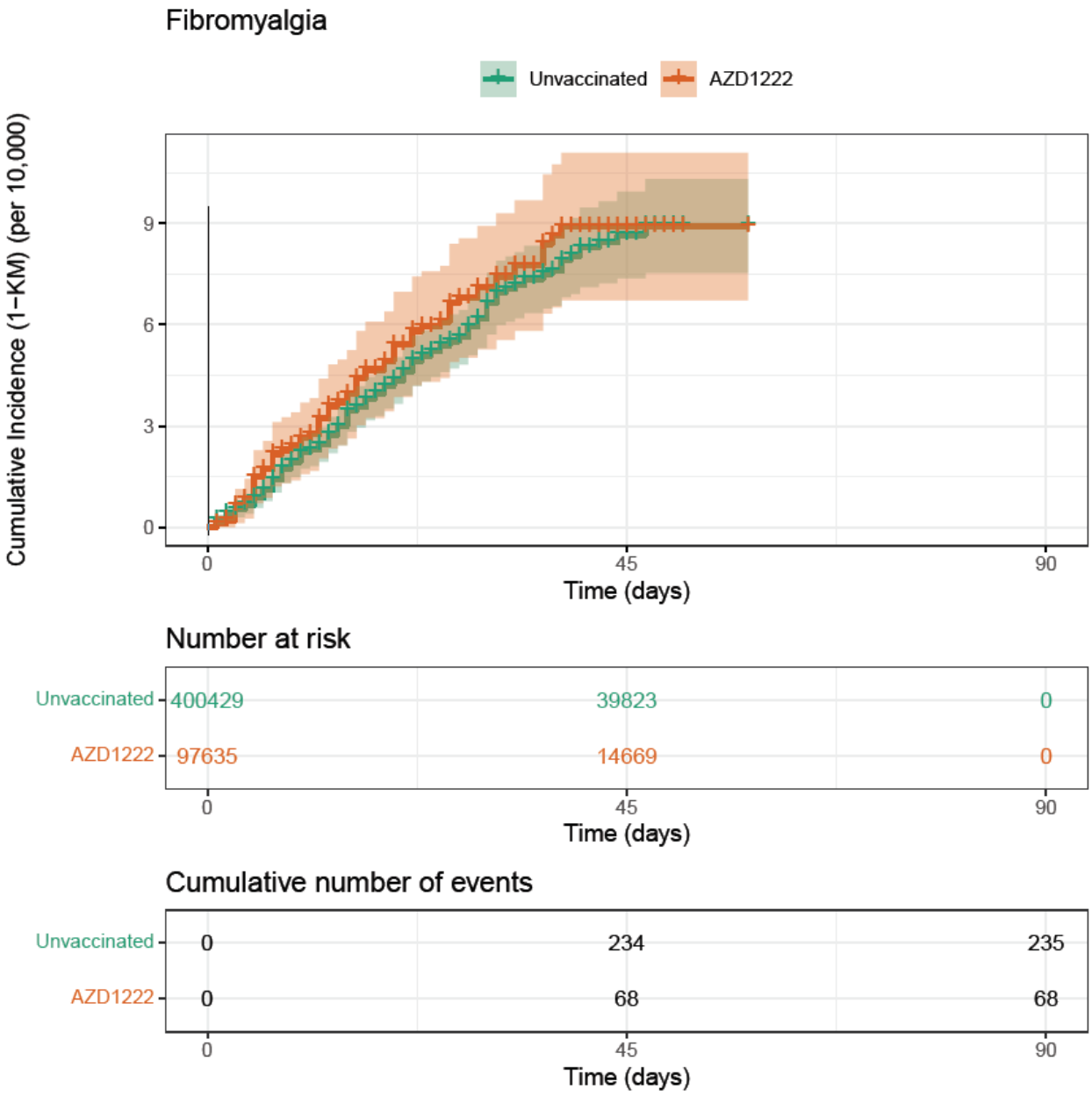

Figure 5.SIDIAP. Anosmia, Ageusia, Cumulative Incidence With Unknown Risk Window

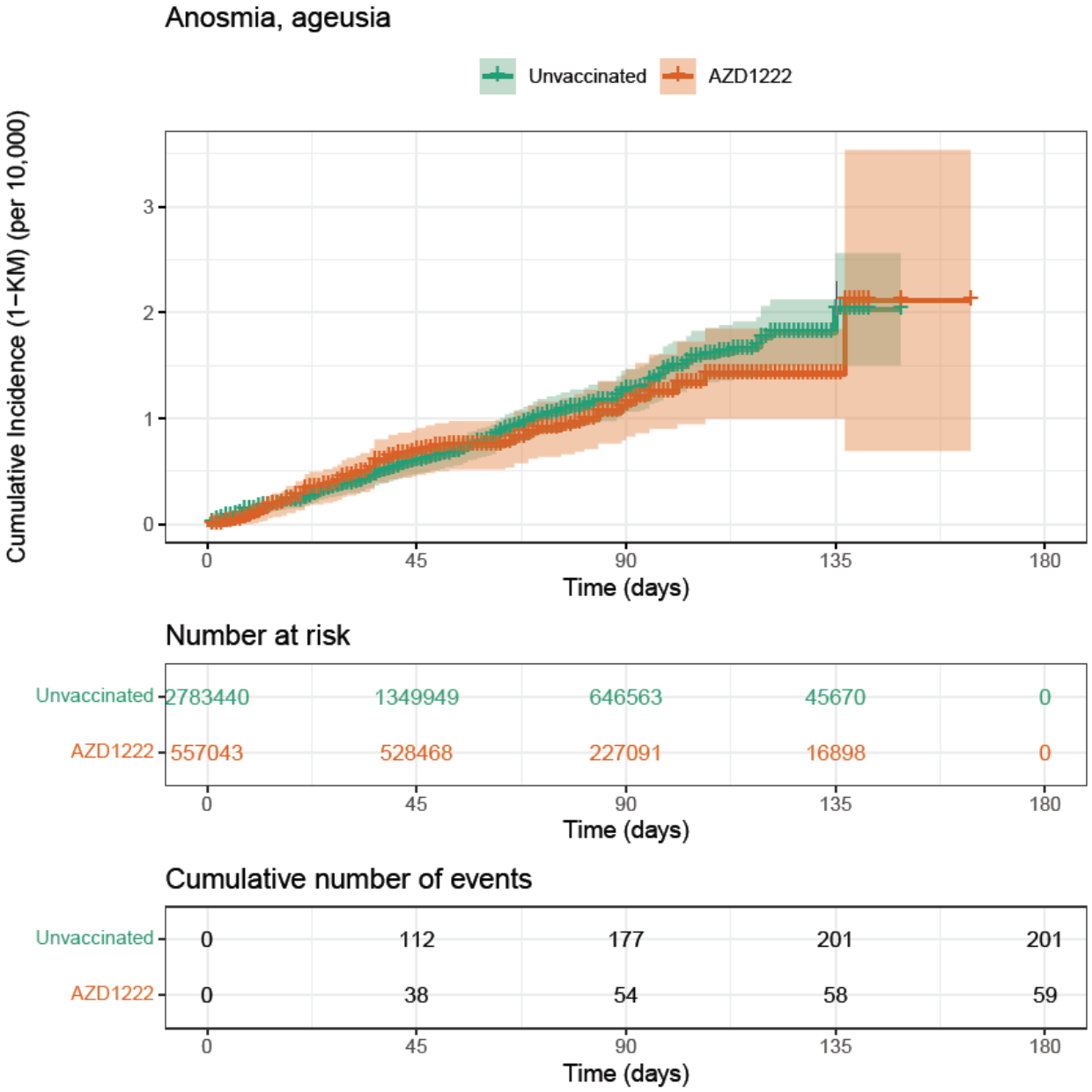

Figure 5.SIDIAP. Type III Hypersensitivity Reactions, Cumulative Incidence With Unknown Risk Window

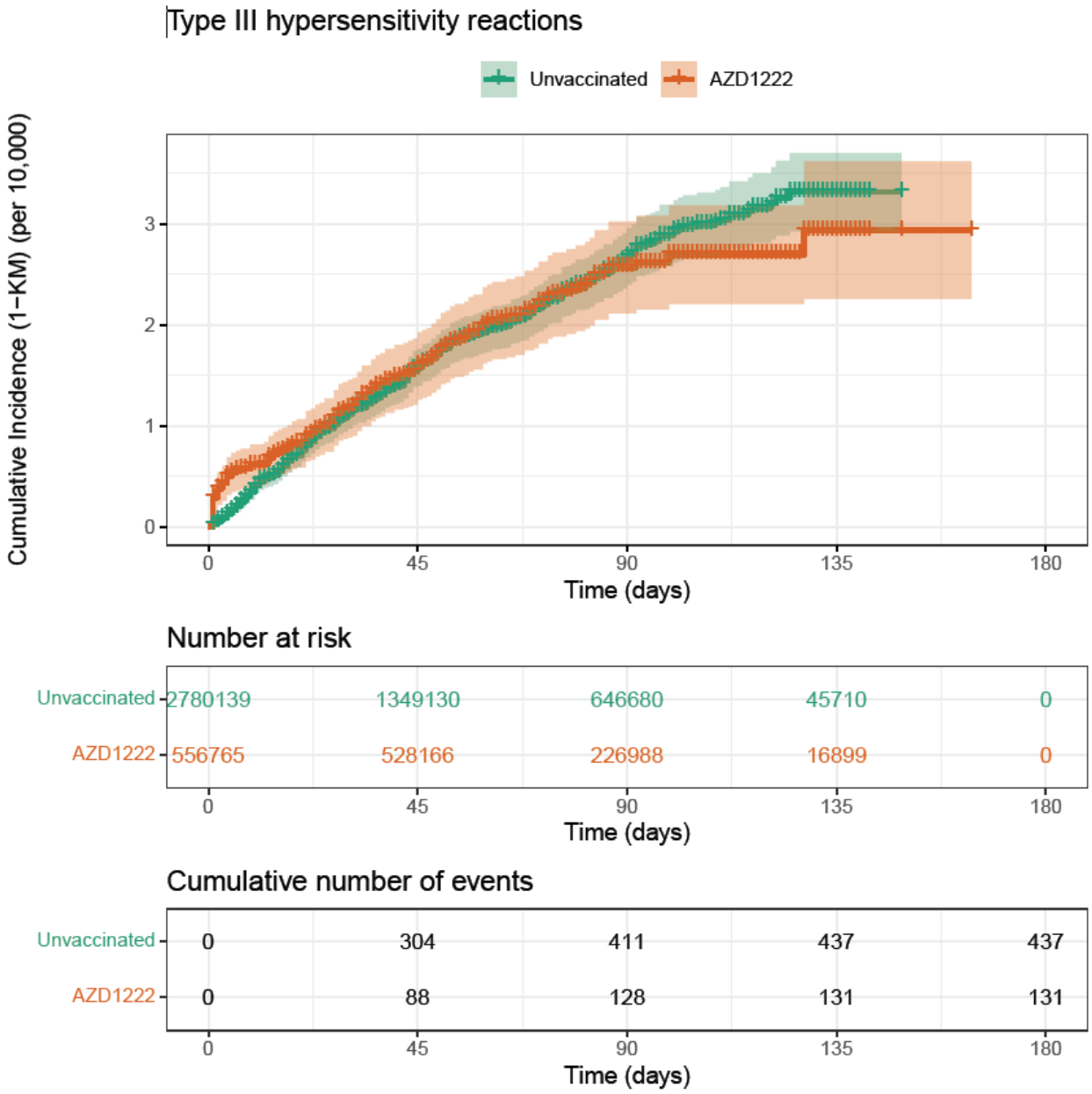

Figure 5.SIDIAP. Vaccine-Associated Enhanced Disease, Including Vaccine-Associated Enhanced Respiratory Disease, Including ARDS, Cumulative Incidence With Unknown Risk Window

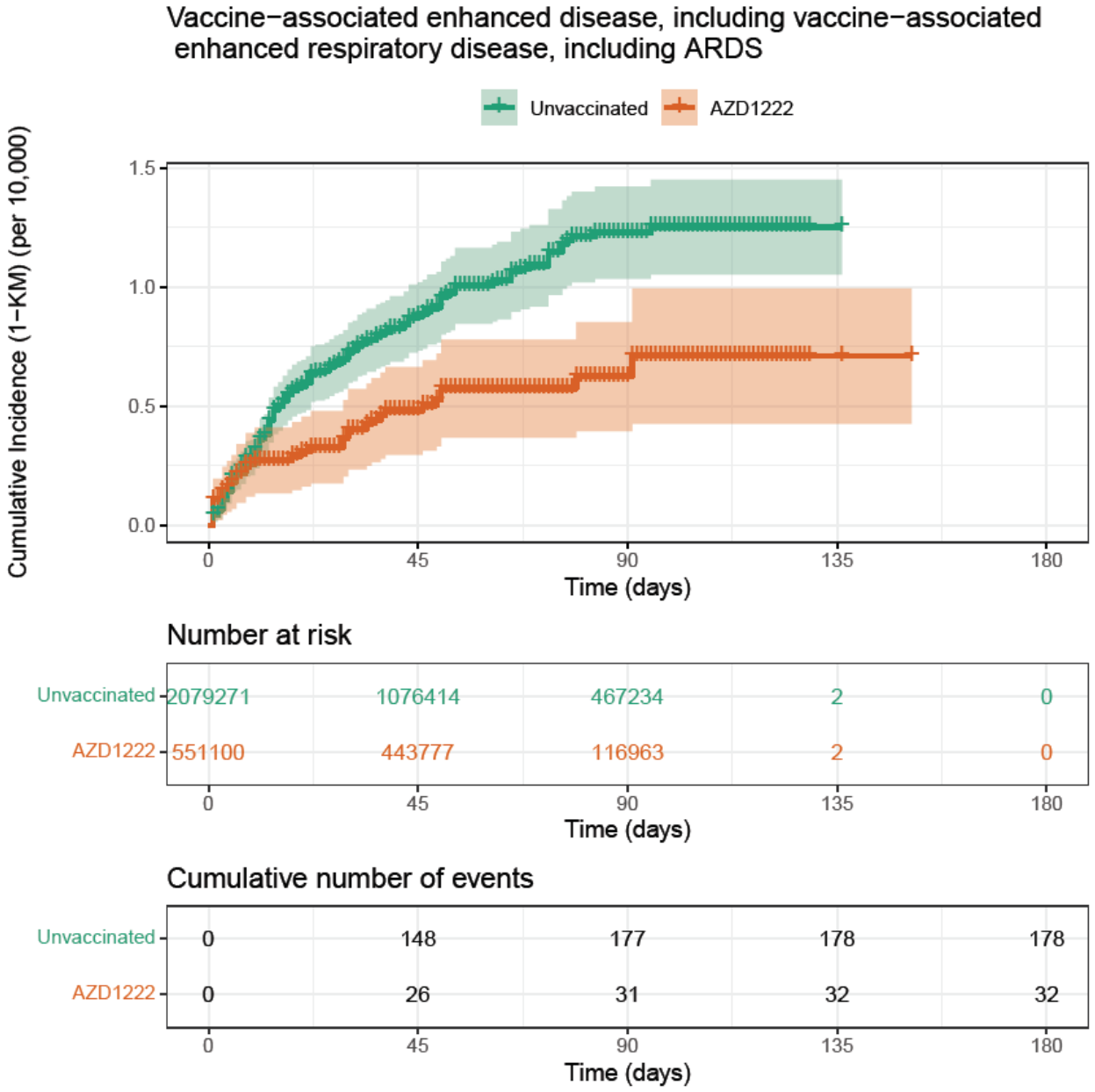

Figure 5.SIDIAP. Erythema Multiforme, Cumulative Incidence With Unknown Risk Window

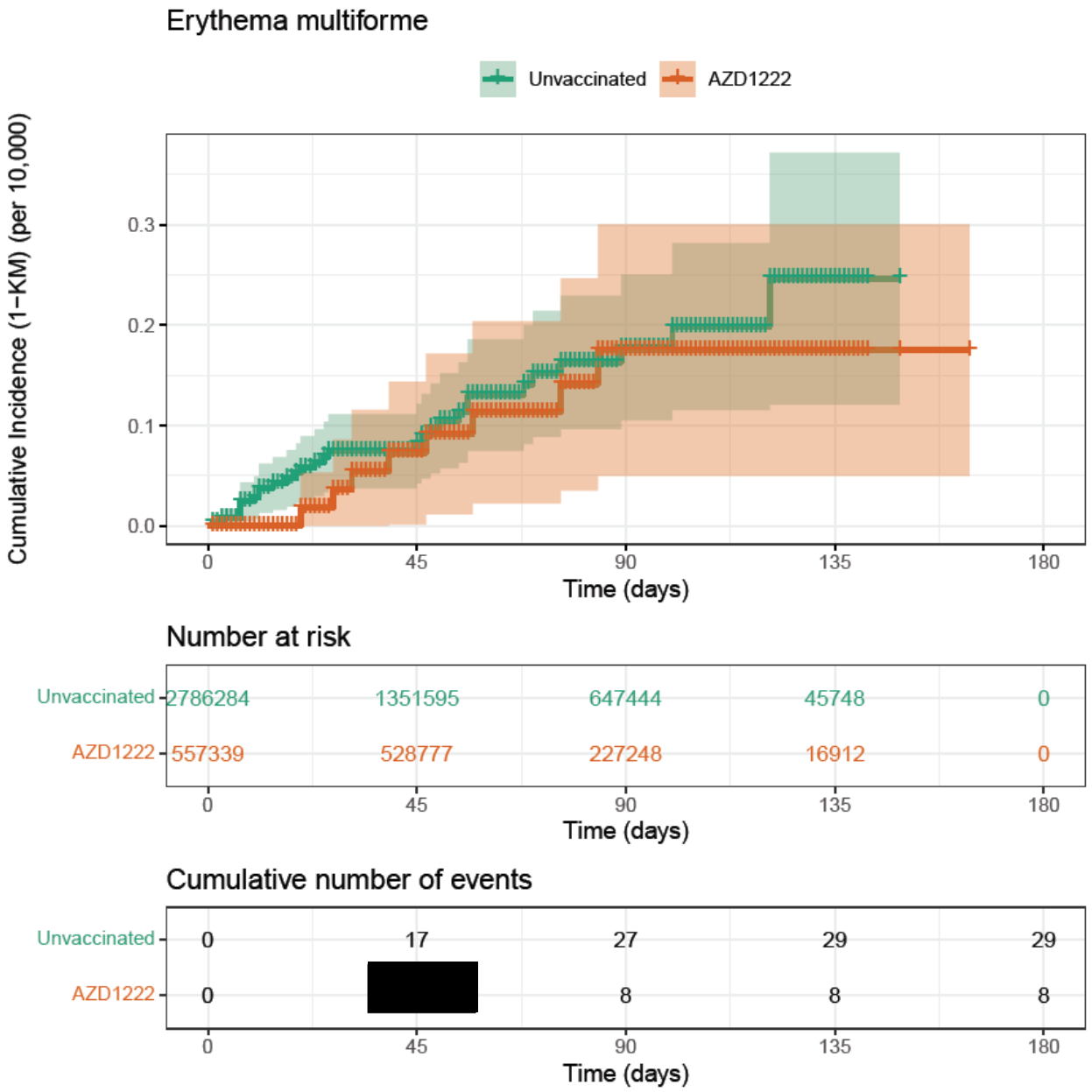

Figure 5.SIDIAP. Chilblain-Like Skin Lesions, Cumulative Incidence With Unknown Risk Window

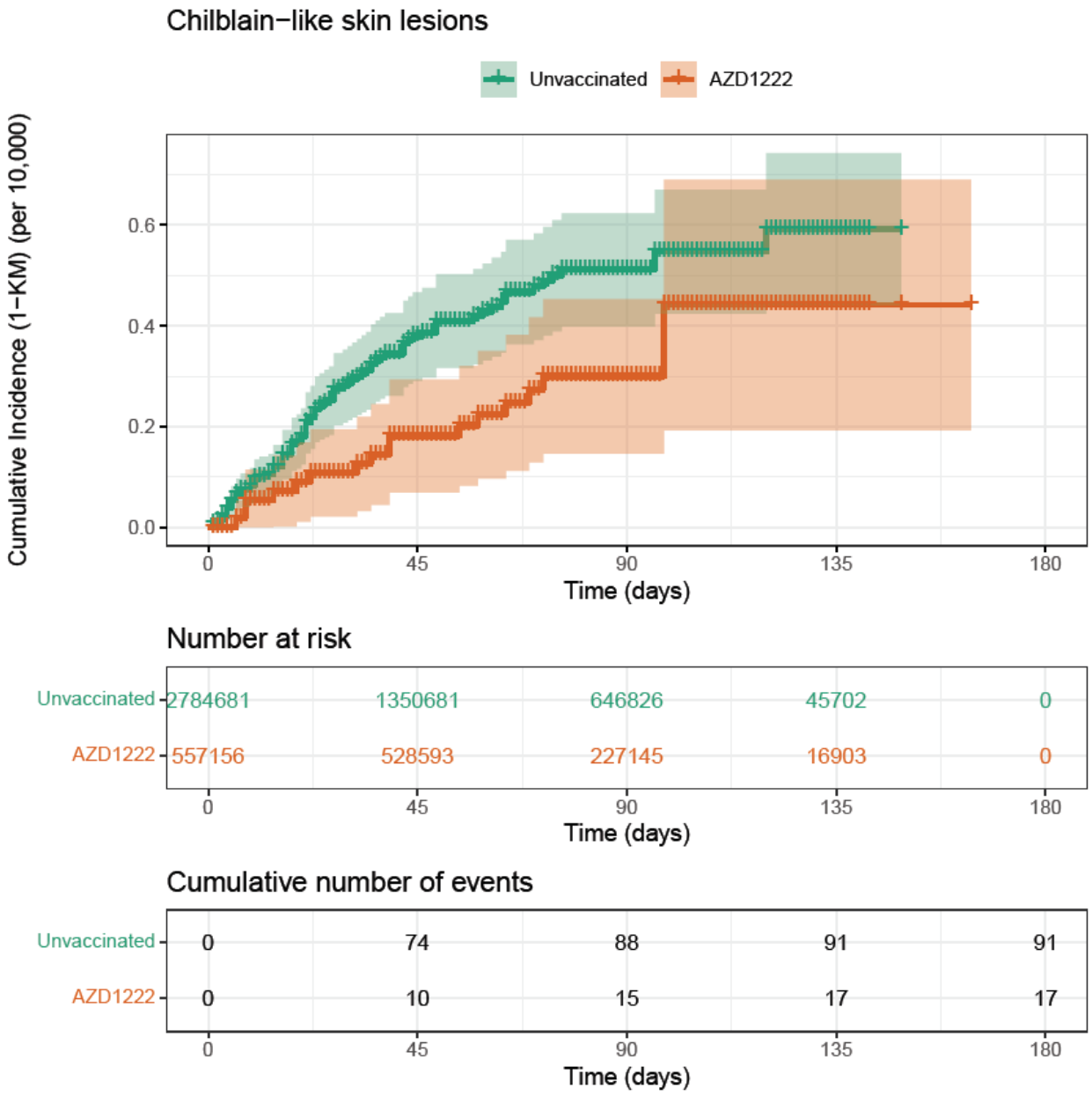

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Table 1.1.ARS. Baseline Characteristics Among the *All Vaccinated Population*, AZD1222 Cohort

	Over all the study period included in interim report 1	
	N	%[a]
Total	342,255	100.00%
Calendar quarter at index date		
Q1 2021	142,284	41.57%
Q2 2021	199,358	58.25%
Q3 2021	613	0.18%
Q4 2021	0	0.00%
Q1 2022	0	0.00%
Q2 2022	0	0.00%
Duration of lookback period (years)		
Mean (SD)	24.94	(10.88)
Median (Q1, Q3)	25	(17,33)
Age at index date (years)		
Mean (SD)	63.17	(13.64)
Median (Q1, Q3)	69	(56,74)
Age groups (years)		
0-11	1	<0.01%
12-15	2	<0.01%
16-19	144	0.04%
20-29	8,397	2.45%
30-39	17,585	5.14%
40-49	36,615	10.70%
50-59	37,334	10.91%
60-69	81,767	23.89%
70-79	160,289	46.83%
80+	121	0.04%
Sex, female	189,071	55.24%
COVID-19 history (diagnosis or test)	10,985	3.21%

N, number; Q1, quartile 1; Q3, quartile 3; SD, standard deviation.
[a] Counts and percentages, unless otherwise specified.

Table 2.1.ARS. Incidence Rates or Prevalence Proportions of AESIs With Well-Defined Risk Window and Cumulative Incidence (1 − KM) of AESIs With Unknown Risk Window Among the *All Vaccinated Population*

		All AZD1222 vaccinated population				
AESI (risk window, days)	Risk esti-mator	N Subjects	N Out-comes	Person-years	Risk per 10,000	95% CI
Myasthenia gravis[a] (1-365)	1-KM	340,771	4	135,026.0	0.12	(0.00-22.31)
Thrombosis without thrombocytopenia[b] (1-42)	IR	340,771	2	71,472.3	0.28	(0.03-1.01)
Thrombosis with thrombocytopenia syndrome[b] (1-42)	IR	340,774	2	71,472.9	0.28	(0.03-1.01)
Narcolepsy[b] (1-42)	IR	340,774	0	71,473.0	0.00	(0.00-0.52)
Thrombocytopenia with associated bleeding[b] (1-42)	IR	340,774	1	71,472.9	0.14	(0.00-0.78)
Autoimmune thyroiditis[a] (1-180)	1-KM	340,478	149	134,806.4	6.72	(0.00-28.77)
Acute aseptic arthritis[b] (1-42)	IR	340,575	52	71,421.8	7.28	(5.44-9.55)
Guillain-Barré syndrome[b] (1-42)	IR	340,769	2	71,472.1	0.28	(0.03-1.01)
Thrombocytopenia[b] (1-42)	IR	340,756	12	71,468.3	1.68	(0.87-2.93)
Capillary leak syndrome[a] (1-365)	1-KM	NA				
Postural orthostatic tachycardia syndrome[b] (1-42)	IR	NA				
Acute cardiac injury including microangiopathy, cardiogenic shock, heart failure[b] (1-90)	IR	340,196	352	130,063.4	27.06	(24.31-30.04)
Stress cardiomyopathy[b] (1-42)	IR	340,750	6	71,467.0	0.84	(0.31-1.83)
Myocardial infarction[b] (1-28)	IR	340,393	110	48,941.8	22.48	(18.47-27.09)
Myocarditis/Pericarditis[b] (1-42)	IR	340,574	49	71,423.3	6.86	(5.08-9.07)
Acute pancreatitis[a] (1-365)	1-KM	340,612	81	134,948.2	2.86	(0.00-25.05)
Acute kidney injury[b] (1-14)	IR	340,592	23	24,893.5	9.24	(5.86-13.86)
Acute liver injury[b] (1-14)	IR	340,757	4	24,907.5	1.61	(0.44-4.11)
Multiple sclerosis, and other demyelinating disorders[a] (1-365)	1-KM	340,759	17	135,017.8	0.59	(0.00-22.78)
Transverse myelitis[b] (1-90)	IR	340,772	2	130,340.0	0.15	(0.02-0.55)
Encephalitis (including ADEM)[b] (1-42)	IR	340,769	4	71,471.6	0.56	(0.15-1.43)

AESI (risk window, days)	Risk esti-mator	All AZD1222 vaccinated population				
		N Subjects	N Out-comes	Person-years	Risk per 10,000	95% CI
Other peripheral and polyneuropathies[b] (1-42)	IR	340,752	9	71,467.3	1.26	(0.58-2.39)
Generalised convulsions[b] (0-14)	IR	340,621	15	26,681.3	5.62	(3.15-9.27)
Optic neuritis/neuromyelitis optica spectrum disorder[b] (1-42)	IR	340,771	2	71,472.2	0.28	(0.03-1.01)
Bell's palsy[b] (1-42)	IR	340,686	18	71,452.7	2.52	(1.49-3.98)
Fibromyalgia[a] (91-365)	1-KM	NA				
Chronic fatigue syndrome/ME/PVFS[a] (183-365)	1-KM	2,044	0	56.6	0.00	(0.00-278.78)
Anosmia, ageusia[a] (1-365)	1-KM	340,774	0	135,028.0	0.00	(0.00-22.19)
Type III hypersensitivity reactions[a] (1-365)	1-KM	340,677	71	134,974.0	2.61	(0.00-24.81)
Anaphylaxis[c] (0-2)	PP	340,775	2	5,357.4	0.06	(0.01-0.21)
Rhabdomyolysis[b] (1-42)	IR	340,754	4	71,468.4	0.56	(0.15-1.43)
Multisystem inflammatory syndrome in adults/children[b] (1-42)	IR	NA				
Sudden death[c] (0-6)	PP	340,781	0	12,496.3	0.00	(0.00-0.11)
Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease, including ARDS[a] (14-365)	1-KM	340,413	20	122,837.8	0.63	(0.00-18.79)
ARDS[b] (1-28)	IR	340,671	6	48,996.0	1.22	(0.45-2.67)
Erythema multiforme[a] (1-365)	1-KM	340,766	12	135,023.1	0.43	(0.00-22.62)
Chilblain-like skin lesions[a] (1-365)	1-KM	340,774	1	135,027.8	0.03	(0.00-22.22)

ADEM, acute disseminated encephalomyelitis; AESI, adverse event of special interest; ARDS, acute respiratory distress syndrome; CI, confidence interval; IR, incidence rate; KM, Kaplan-Meier; ME, myalgic encephalitis; N, number; NA, not available; PR, prevalence rate; PVFS, postviral fatigue syndrome; PY, person-years.

[a] Cumulative incidence (1-KM) per 10,000, for these outcomes with unknown risk windows

[b] Incidence rate (IR) per 10,000 person-years, for outcomes with well-defined risk windows

[c] Prevalence proportion (PP) per 10,000, for outcomes with well-defined and very short risk windows

Table 2.ARS. TTS. Cumulative Incidence (1 − KM) of Thrombosis With Thrombocytopenia Syndrome Among the *All Vaccinated Population*, by Age Groups and Sex

	All AZD1222 vaccinated population				
Thrombosis with thrombocytopenia syndrome	**N Subjects**	**N Outcomes**	**Person-years**	**1 − KM per 10,000**	**95% CI**
By age groups (years)					
0-11	1	0	0.1	0.00	(0.00-6825.00)
12-15	2	0	0.1	0.00	(0.00-5245.32)
16-19	144	0	22.3	0.00	(0.00-803.25)
20-29	8,218	0	1,691.5	0.00	(0.00-149.81)
30-39	17,303	0	3,646.2	0.00	(0.00-95.82)
40-49	36,353	0	7,253.6	0.00	(0.00-71.11)
50-59	37,173	1	7,599.8	0.27	(0.00-70.64)
60-69	81,467	0	15,572.9	0.00	(0.00-47.58)
70-79	159,993	1	35,661.4	0.06	(0.00-34.02)
80+	120	0	24.9	0.00	(0.00-1057.20)
By sex					
Male	152,355	0	31,618.5	0.00	(0.00-34.79)
Female	188,419	2	39,854.4	0.11	(0.00-31.39)

CI, confidence interval; KM, Kaplan-Meier; N, number; PY, person-years.
[a] Numbers correspond to counts and percentages unless otherwise specified.

Table 3.1.ARS. Description of the Utilisation Pattern of Subsequent Doses of a COVID-19 Vaccine in the *All Vaccinated First Dose Population*, Over All the Study Period

AZD1222 cohort	Over all the study period included in interim report 1[a]	
	N	%
Subjects with a first dose of AZD1222 (Vaxzevria)	342,030	
Subjects who had received only a first dose of AZD1222 at the end of study period for interim report 1	12,138	3.55%
Subjects with a first dose of AZD122 who receive a second dose of any COVID-19 vaccine and time between doses	329,892	96.45%
Vaxzevria (COVID-19 Vaccine AstraZeneca)	313,454	91.65%
Time between dose 1 and dose 2, weeks		
Mean (SD)	11.92	(0.44)
Median (Q1-Q3)	12.0	(12.0, 12.0)
min, max	3,	26
<2 weeks	0	0.00%
2-4 weeks	3	<0.01%
5-8 weeks	333	0.11%
9-12 weeks	310,863	99.17%
13-18 weeks	2,177	0.69%
>18 weeks	78	0.02%
Comirnaty (COVID-19 Vaccine Pfizer-BioNTech)	14,188	4.15%
Time between dose 1 and dose 2, weeks		
Mean (SD)	12.45	(2.50)
Median (Q1-Q3)	12.0	(12.0, 12.0)
min, max	2,	29
<2 weeks	0	0.00%
2-4 weeks	16	0.11%
5-8 weeks	237	1.67%
9-12 weeks	12,511	88.18%
13-18 weeks	870	6.13%
>18 weeks	554	3.90%

AZD1222 cohort	Over all the study period included in interim report 1[a]	
	N	%
Spikevax (COVID-19 Vaccine Moderna)	2,239	0.65%
Time between dose 1 and dose 2, weeks		
Mean (SD)	12.70	(3.11)
Median (Q1-Q3)	12.0	(12.0, 12.0)
min, max	4,	28
<2 weeks	0	0.00%
2-4 weeks	3	0.13%
5-8 weeks	44	1.97%
9-12 weeks	1,920	85.75%
13-18 weeks	125	5.58%
>18 weeks	147	6.57%
COVID-19 Vaccine Janssen	11	<0.01%
Time between dose 1 and dose 2, weeks		
Mean (SD)	15.19	(4.12)
Median (Q1-Q3)	15.9	(12.8, 17.0)
min, max	7,	23
<2 weeks	0	0.00%
2-4 weeks	0	0.00%
5-8 weeks	1	9.09%
9-12 weeks	2	18.18%
13-18 weeks	7	63.64%
>18 weeks	1	9.09%
Other COVID-19 vaccines	0	0.00%
Time between dose 1 and dose 2, weeks		
Mean (SD)		
Median (Q1-Q3)		
min, max		
<2 weeks	0	0.00%
2-4 weeks	0	0.00%
5-8 weeks	0	0.00%
9-12 weeks	0	0.00%
13-18 weeks	0	0.00%
>18 weeks	0	0.00%

AZD1222 cohort	Over all the study period included in interim report 1[a]	
	N	%
Subjects with a first and second dose of AZD122 who receive a third dose of any COVID-19 vaccine and time between doses	11	<0.01%
Vaxzevria (COVID-19 Vaccine AstraZeneca)	4	<0.01%
Time between dose 2 and dose 3		
Mean (SD)	5.36	(2.34)
Median (Q1-Q3)	4.9	(3.8, 6.0)
min, max	3,	8
<12 weeks	4	100.00%
12-24 weeks	0	0.00%
25-37 weeks	0	0.00%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%
Comirnaty (COVID-19 Vaccine Pfizer-BioNTech)	5	<0.01%
Time between dose 2 and dose 3		
Mean (SD)	6.89	(5.75)
Median (Q1-Q3)	4.4	(3.3, 8.0)
min, max	2,	16
<12 weeks	4	80.00%
12-24 weeks	1	20.00%
25-37 weeks	0	0.00%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%
Spikevax (COVID-19 Vaccine Moderna)	2	<0.01%
Time between dose 2 and dose 3		
Mean (SD)	7.64	(6.36)
Median (Q1-Q3)	7.6	(5.4, 9.0)
min, max	3,	12
<12 weeks	1	50.00%
12-24 weeks	1	50.00%
25-37 weeks	0	0.00%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%

AZD1222 cohort	Over all the study period included in interim report 1[a]	
	N	%
COVID-19 Vaccine Janssen	0	0.00%
Time between dose 2 and dose 3		
Mean (SD)		
Median (Q1-Q3)		
min, max		
<12 weeks	0	0.00%
12-24 weeks	0	0.00%
25-37 weeks	0	0.00%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%
Other COVID-19 vaccines	0	0.00%
Time between dose 2 and dose 3		
Mean (SD)		
Median (Q1-Q3)		
min, max		
<12 weeks	0	0.00%
12-24 weeks	0	0.00%
25-37 weeks	0	0.00%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%

Q1 = Quartile 1; Q3 = Quartile 3; SD = Standard deviation

Table 4.ARS. Cohort Attrition for the *Matched Population*

Cohort design	N	(%)
AZD1222 COHORT		
All vaccinated population	342,255	
All vaccinated first dose population	342,030	(99.93%)
And with at least 12 months lookback period (eligible to be matched)	336,792	(98.47%)
Unique vaccinated subjects not matched	0	(0.00%)
Unique vaccinated subjects matched	336,792	(100.00%)
Matching ratio 1:1	0	(0.00%)
Matching ratio 1:2	1	(<0.01%)
Matching ratio 1:3	0	(0.00%)
Matching ratio 1:4	2	(<0.01%)
Matching ratio 1:5	336,789	(100.00%)
UNVACCINATED COHORT		
Unique subjects with no record of vaccination with any COVID-19 vaccine during the study period	3,603,951	
And with at least 12 months lookback period (eligible to be matched)	3,415,228	(94.76%)
Unique unvaccinated subjects matched	965,953	(28.28%)
Unique unvaccinated subjects not matched	2,449,275	(71.72%)
Non-unique unvaccinated subjects matched	1,683,955	
Number of times an unvaccinated subject was matched		
Median (Q1-Q3)	1	(1-2)
Min-Max		1-14
1	577,475	(59.78%)
2	210,862	(21.83%)
3	93,229	(9.65%)
4	45,250	(4.68%)
5 or more	39,137	(4.05%)

N = number; Q1 = Quartile 1; Q3 = Quartile 3

Table 5.ARS. Reasons for Censoring Follow-Up Among the *Matched Population* Cohorts

	AZD1222 cohort		Unvaccinated cohort	
Cohort design	**N**	**(%)**	**N**	**(%)**
Total	336,792	(100.00%)	1,683,955	(100.00%)
Person-months of follow-up				
Mean follow-up (SD), months	4.73	(1.07)	2.17	(1.91)
Median follow-up (Q1-Q3), months	4.9	(4.0-5.4)	1.4	(0.5-3.6)
P1 - P99 follow-up, months	2.7	-6.6	<0.1	-6.5
Received AZD1222, n (%)	0	(0.00%)	254,542	(15.12%)
Received any COVID-19 vaccine other than AZD1222, n (%)	15,805	(4.69%)	1,079,817	(64.12%)
Censored 365 days after the second dose of AZD1222, n (%)	0	(0.00%)	0	(0.00%)
End of study period, n (%)	318,996	(94.72%)	336,089	(19.96%)
Enrolment termination date in the health plan or system, n(%)	1,656	(0.49%)	8,740	(0.52%)
Death, n(%)	335	(0.10%)	4,767	(0.28%)

N = number; Q1 = Quartile 1; Q3 = Quartile 3

Table 11.1.ARS. Crude Risk Estimates for AESIs in the *Matched Cohorts* Based on Definition and Duration of Risk Windows

		AZD1222 cohort					Unvaccinated cohort				
AESI (risk window, days)	**Risk esti-mator**	**N Patients**	**N Out-comes**	**Person-years**	**Risk per 10,000**	**95% CI**	**N Patients**	**N Out-comes**	**Person-years**	**Risk per 10,000**	**95% CI**
Myasthenia gravis[a] (1-365)	1-KM	336,782	4	133,490.8	0.12	(0.00-22.44)	1,683,625	10	306,480.1	0.14	(0.00-10.12)
Thrombosis without thrombocytopenia[b] (1-42)	IR	336,782	2	70,705.7	0.28	(0.03-1.02)	1,683,747	4	186,984.4	0.21	(0.03-1.52)
Thrombosis with thrombocytopenia syndrome[b] (1-42)	IR	336,785	2	70,706.3	0.28	(0.03-1.02)	1,683,765	7	186,986.4	0.37	(0.10-1.35)
Narcolepsy[b] (1-42)	IR	336,785	0	70,706.4	0.00	(0.00-0.52)	1,683,778	0	186,988.4		NR
Thrombocytopenia with associated bleeding[b] (1-42)	IR	336,785	1	70,706.3	0.14	(0.00-0.79)	1,683,757	10	186,985.5	0.53	(0.19-1.51)
Autoimmune thyroiditis[a] (1-180)	1-KM	336,498	146	133,277.1	6.69	(0.00-28.87)	1,680,991	490	305,716.4	8.71	(0.00-18.75)
Acute aseptic arthritis[b] (1-42)	IR	336,588	52	70,655.6	7.36	(5.50-9.65)	1,681,472	131	186,762.7	7.01	(5.48-8.97)
Guillain-Barré syndrome[b] (1-42)	IR	336,780	2	70,705.5	0.28	(0.03-1.02)	1,683,670	8	186,974.8	0.43	(0.14-1.28)
Thrombocytopenia[b] (1-42)	IR	336,769	11	70,702.0	1.56	(0.78-2.78)	1,683,316	91	186,930.3	4.87	(3.42-6.93)
Capillary leak syndrome[a] (1-365)	1-KM	NA					NA				
Postural orthostatic tachycardia syndrome[b] (1-42)	IR	NA					NA				

AESI (risk window, days)	Risk esti-mator	AZD1222 cohort					Unvaccinated cohort				
		N Patients	N Out-comes	Person-years	Risk per 10,000	95% CI	N Patients	N Out-comes	Person-years	Risk per 10,000	95% CI
Acute cardiac injury including microangiopathy, cardiogenic shock, heart failure[b] (1-90)	IR	336,208	350	128,616.5	27.21	(24.44-30.22)	1,670,371	1,816	294,262.0	61.71	(56.83-67.01)
Stress cardiomyopathy[b] (1-42)	IR	336,761	5	70,700.5	0.71	(0.23-1.65)	1,683,453	15	186,954.7	0.80	(0.43-1.50)
Myocardial infarction[b] (1-28)	IR	336,408	109	48,417.0	22.51	(18.49-27.16)	1,677,257	421	138,257.4	30.45	(26.58-34.88)
Myocarditis/Pericarditis[b] (1-42)	IR	336,585	47	70,656.9	6.65	(4.89-8.85)	1,680,385	337	186,636.8	18.06	(15.18-21.48)
Acute pancreatitis[a] (1-365)	1-KM	336,624	80	133,413.4	2.86	(0.00-25.19)	1,681,884	173	306,208.4	2.39	(0.00-12.39)
Acute kidney injury[b] (1-14)	IR	336,605	23	24,625.2	9.34	(5.92-14.01)	1,679,406	273	77,108.3	35.40	(30.18-41.54)
Acute liver injury[b] (1-14)	IR	336,768	4	24,639.1	1.62	(0.44-4.16)	1,683,447	16	77,291.4	2.07	(1.17-3.68)
Multiple sclerosis, and other demyelinating disorders[a] (1-365)	1-KM	336,770	16	133,483.1	0.57	(0.00-22.89)	1,683,264	100	306,386.6	2.05	(0.00-12.04)
Transverse myelitis[b] (1-90)	IR	336,783	2	128,892.0	0.16	(0.02-0.56)	1,683,744	3	296,228.5	0.10	(0.02-0.44)
Encephalitis (including ADEM)[b] (1-42)	IR	336,780	4	70,705.0	0.57	(0.15-1.45)	1,683,690	14	186,977.1	0.75	(0.38-1.49)
Other peripheral and polyneuropathies[b] (1-42)	IR	336,763	9	70,700.7	1.27	(0.58-2.42)	1,683,061	43	186,915.4	2.30	(1.39-3.80)

AESI (risk window, days)	Risk esti-mator	AZD1222 cohort					Unvaccinated cohort				
		N Patients	N Out-comes	Person-years	Risk per 10,000	95% CI	N Patients	N Out-comes	Person-years	Risk per 10,000	95% CI
Generalised convulsions[b] (0-14)	IR	336,631	15	26,393.6	5.68	(3.18-9.37)	1,680,789	133	83,281.0	15.97	(12.66-20.15)
Optic neuritis/neuromyelitis optica spectrum disorder[b] (1-42)	IR	336,782	2	70,705.6	0.28	(0.03-1.02)	1,683,725	6	186,979.4	0.32	(0.13-0.81)
Bell's palsy[b] (1-42)	IR	336,697	18	70,686.1	2.55	(1.51-4.02)	1,682,830	56	186,887.2	3.00	(2.04-4.41)
Fibromyalgia[a] (91-365)	1-KM	NA					NA				
Chronic fatigue syndrome/ME/PVFS[a] (183-365)	1-KM	1,585	0	44.5	0.00	(0.00-316.59)	2,793	0	76.5	0.00	(0.00-238.49)
Anosmia, ageusia[a] (1-365)	1-KM	336,785	0	133,492.8	0.00	(0.00-22.32)	1,683,773	0	306,501.9	0.00	(0.00-9.98)
Type III hypersensitivity reactions[a] (1-365)	1-KM	336,690	69	133,439.8	2.57	(0.00-24.90)	1,681,718	499	306,112.7	6.18	(0.00-16.18)
Anaphylaxis[c] (0-2)	PP	336,785	2	5,299.4	0.06	(0.01-0.21)	1,683,886	0	18,232.5	0.00	(0.00-0.02)
Rhabdomyolysis[b] (1-42)	IR	336,765	3	70,701.8	0.42	(0.09-1.24)	1,683,501	37	186,957.6	1.98	(1.14-3.42)
Multisystem inflammatory syndrome in adults/children[b] (1-42)	IR	NA					NA				
Sudden death[c] (0-6)	PP	336,791	0	12,361.3	0.00	(0.00-0.11)	1,683,944	1	41,201.0	0.01	(0.00-0.03)

AESI (risk window, days)	Risk esti-mator	AZD1222 cohort					Unvaccinated cohort				
		N Patients	N Out-comes	Person-years	Risk per 10,000	95% CI	N Patients	N Out-comes	Person-years	Risk per 10,000	95% CI
Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease, including ARDS[a] (14-365)	1-KM	335,408	20	121,145.2	0.64	(0.00-18.93)	1,332,697	146	252,403.8	2.15	(0.00-11.34)
ARDS[b] (1-28)	IR	336,682	6	48,470.5	1.24	(0.45-2.69)	1,682,532	105	138,649.1	7.57	(5.60-10.24)
Erythema multiforme[a] (1-365)	1-KM	336,777	12	133,487.8	0.43	(0.00-22.75)	1,683,637	20	306,474.5	0.26	(0.00-10.24)
Chilblain-like skin lesions[a] (1-365)	1-KM	336,785	1	133,492.6	0.03	(0.00-22.35)	1,683,778	0	306,502.7	0.00	(0.00-9.98)

ADEM, acute disseminated encephalomyelitis; AESI, adverse event of special interest; ARDS, acute respiratory distress syndrome; CI, confidence interval; IR, incidence rate; KM, Kaplan-Meier; ME, myalgic encephalitis; N, number; NA, not available; NR, not reportable; PR, prevalence rate; PVFS, postviral fatigue syndrome; PY, person-years.

[a] Cumulative incidence (1-KM) per 10,000, for these outcomes with unknown risk windows

[b] Incidence rate (IR) per 10,000 person-years, for outcomes with well-defined risk windows

[c] Prevalence proportion (PP) per 10,000, for outcomes with well-defined and very short risk windows

Figure1.ARS. Number of Subjects Vaccinated With a First Dose of AZD1222 Who Were Excluded, Included, and Could Be Matched by Calendar Time

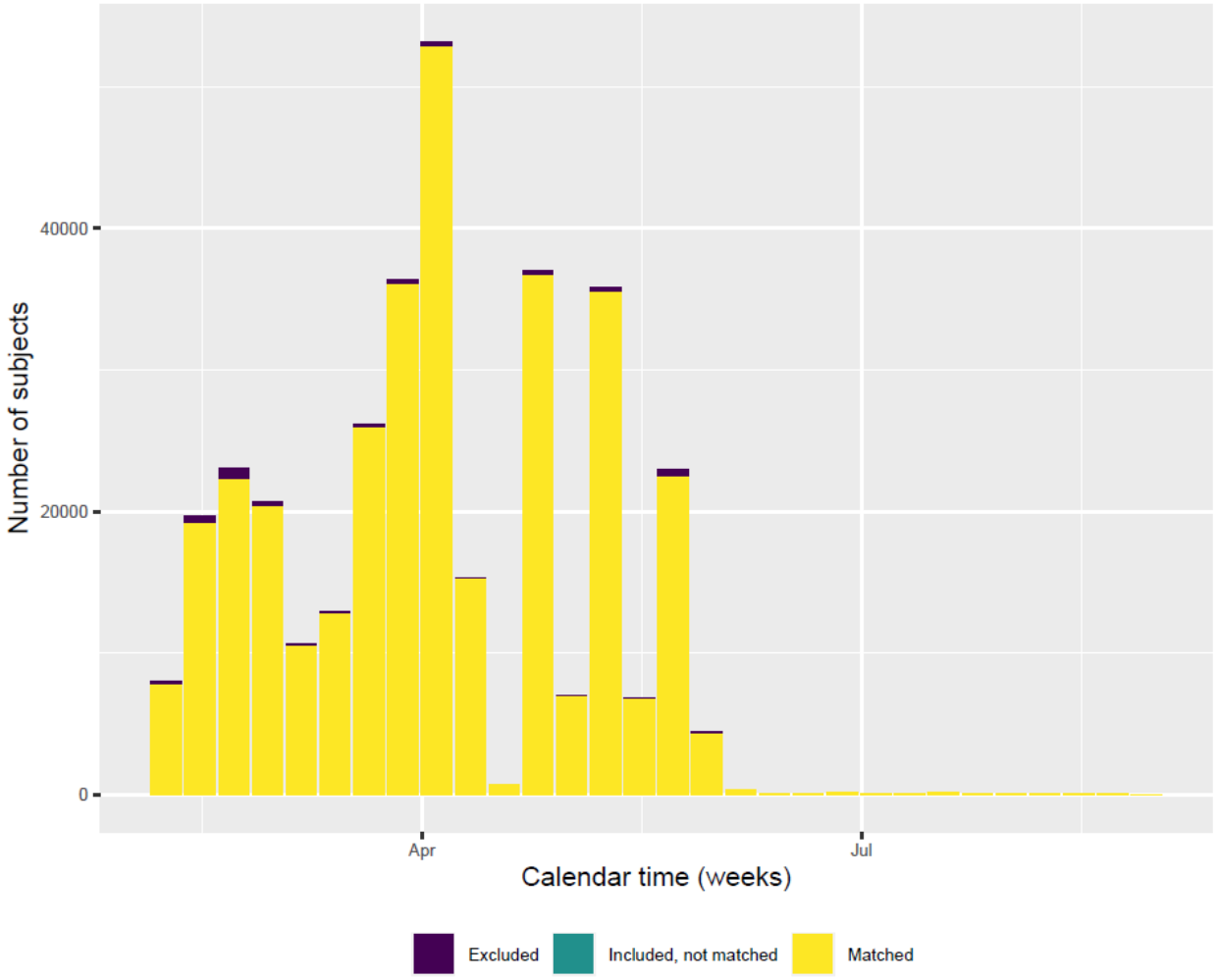


Figure2.ARS. AZD1222 Cohort, Reasons for Censoring Follow-up, by Quarter

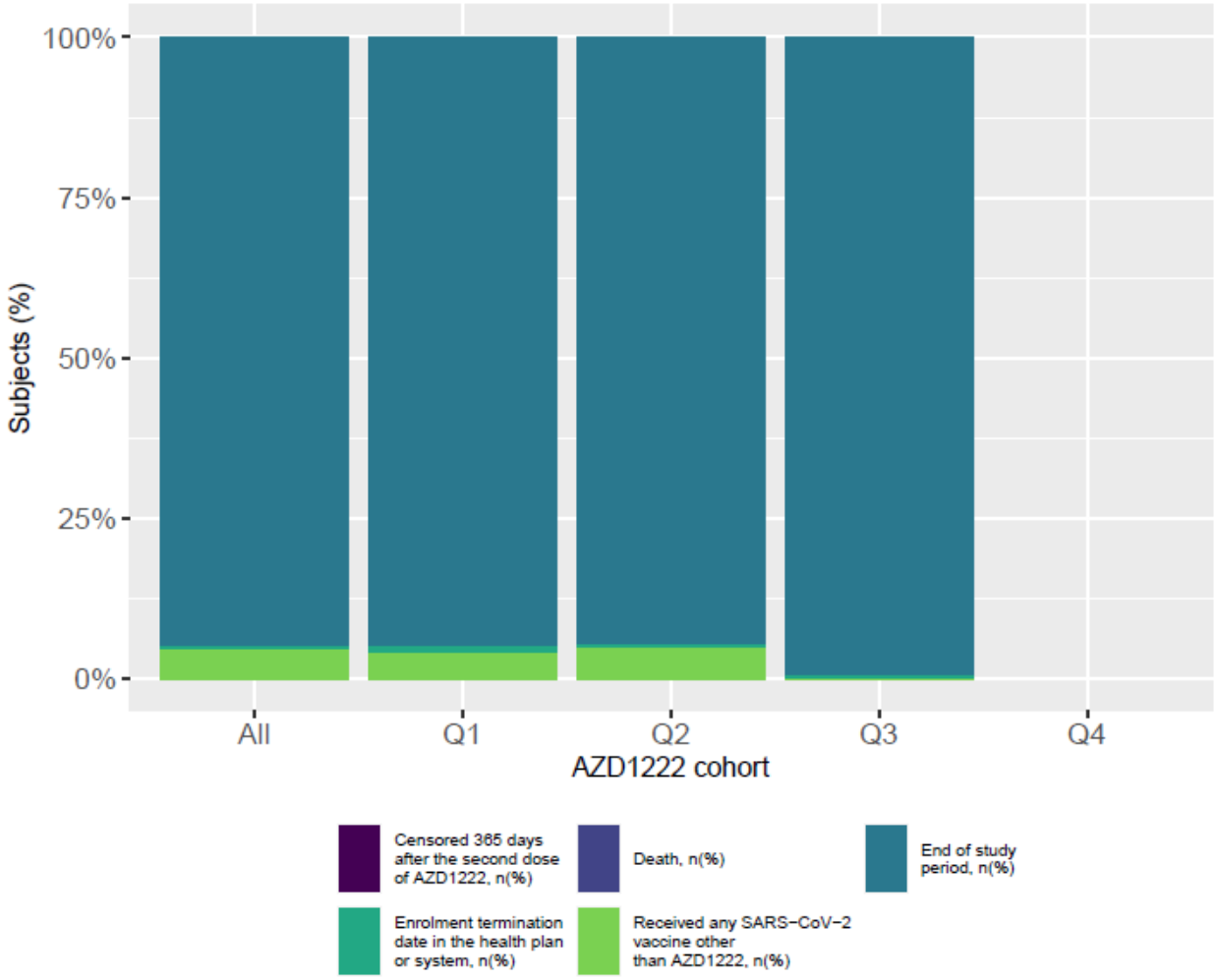


Figure2.ARS. Unvaccinated Cohort, Reasons for Censoring Follow-up, by Quarter

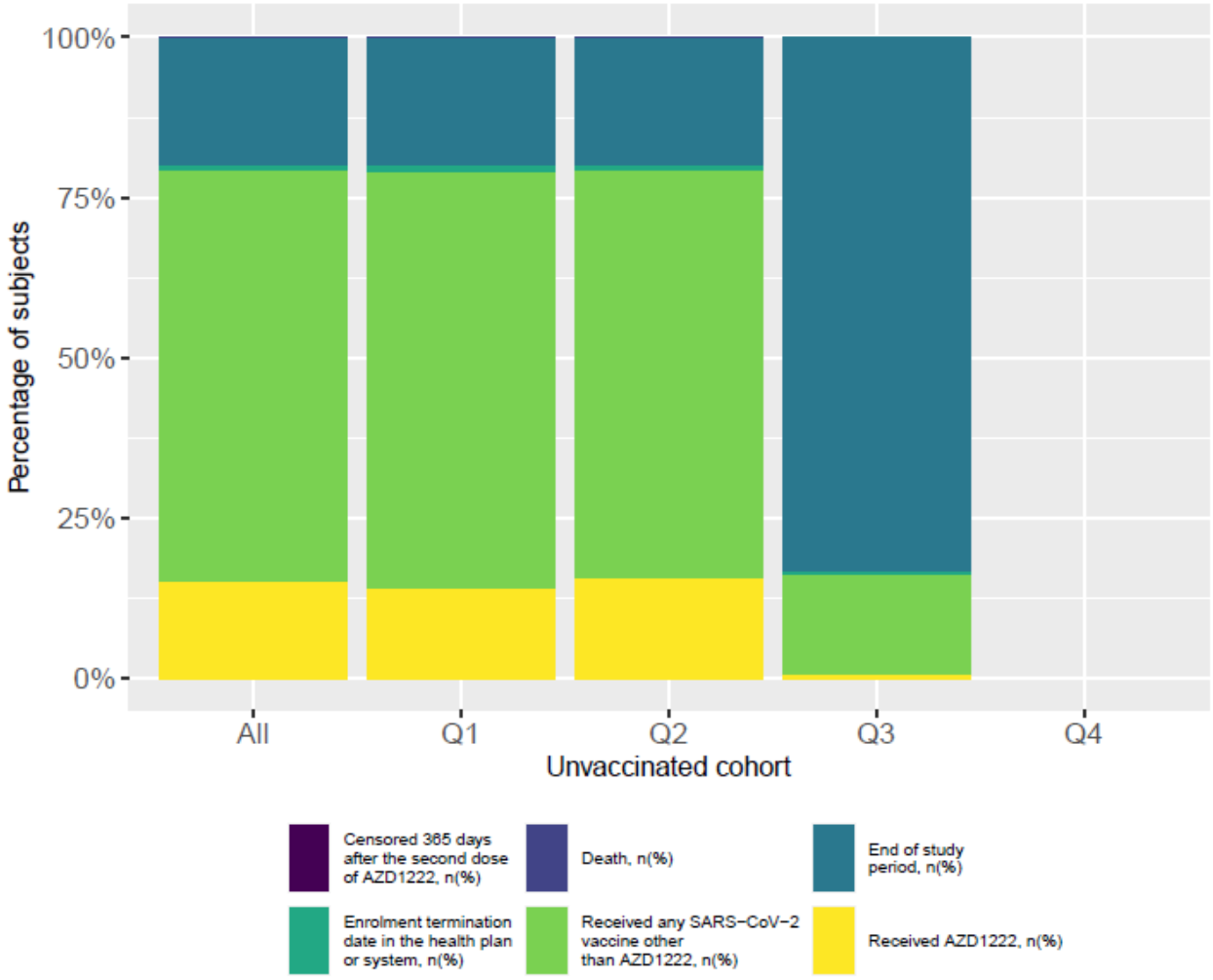


Figure 5.ARS. Myasthenia Gravis, Cumulative Incidence With Unknown Risk Window

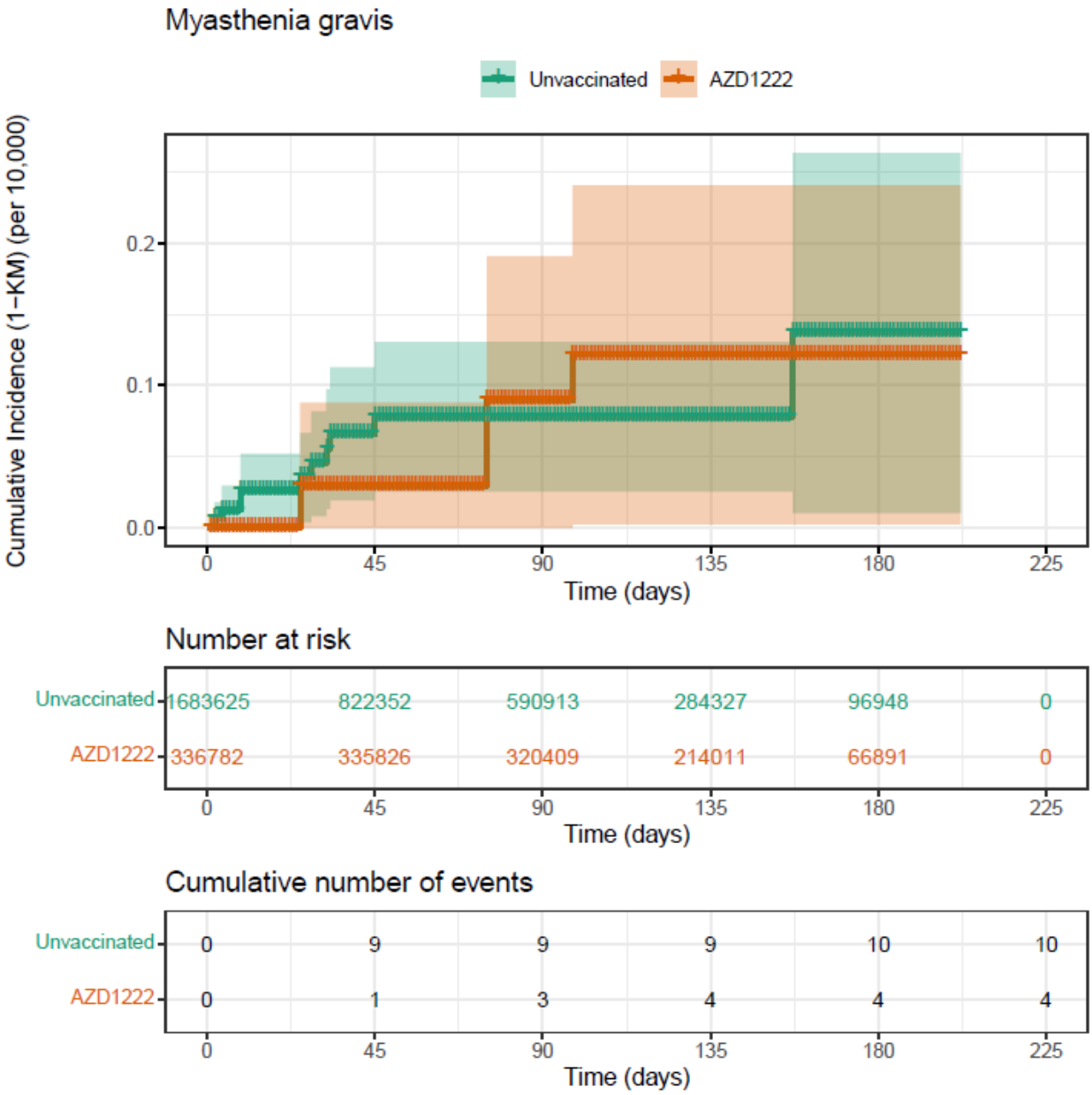


Figure 5.ARS. Autoimmune Thyroiditis, Cumulative Incidence With Unknown Risk Window

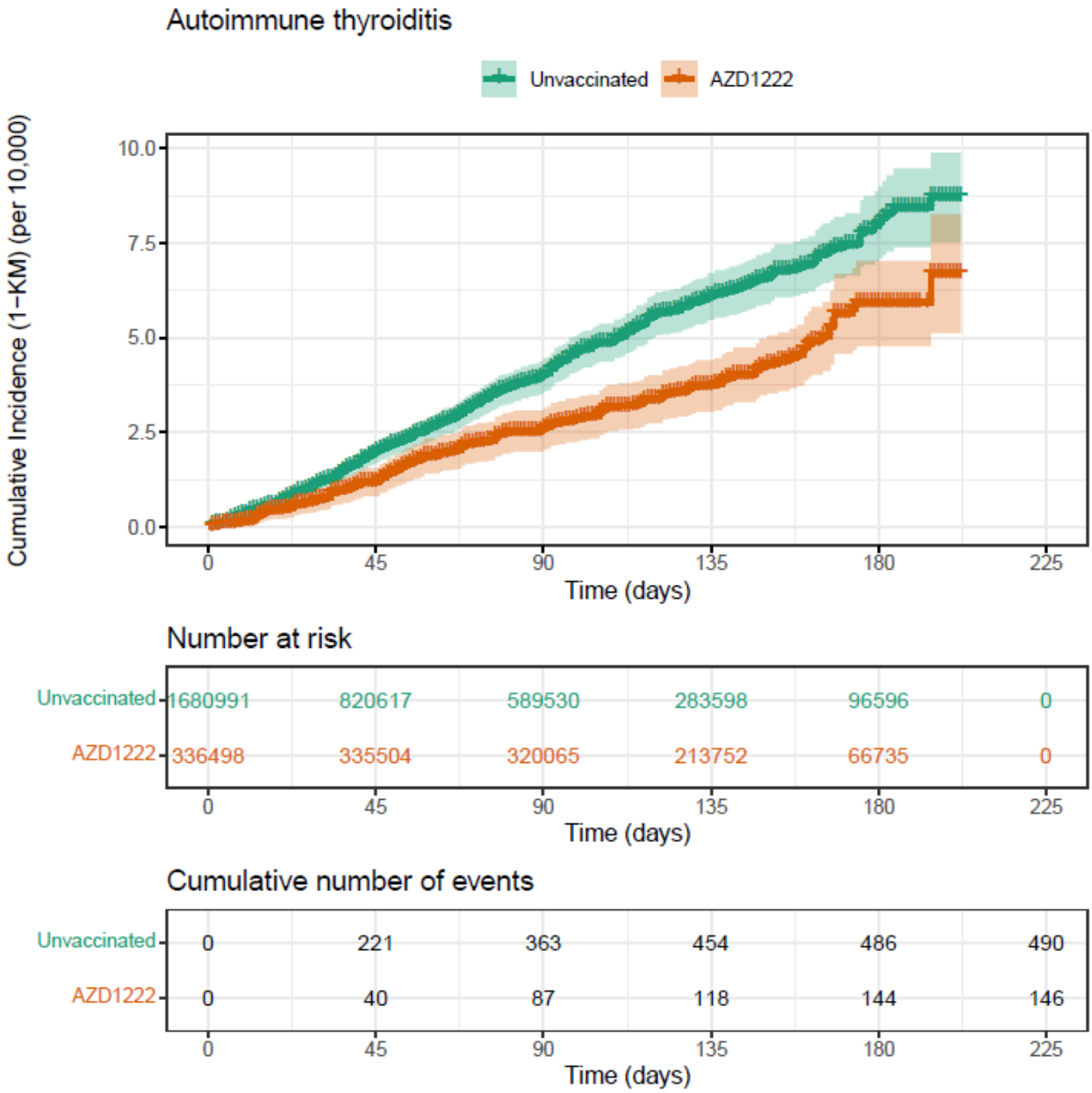


Figure 5.ARS. Acute Pancreatitis, Cumulative Incidence With Unknown Risk Window

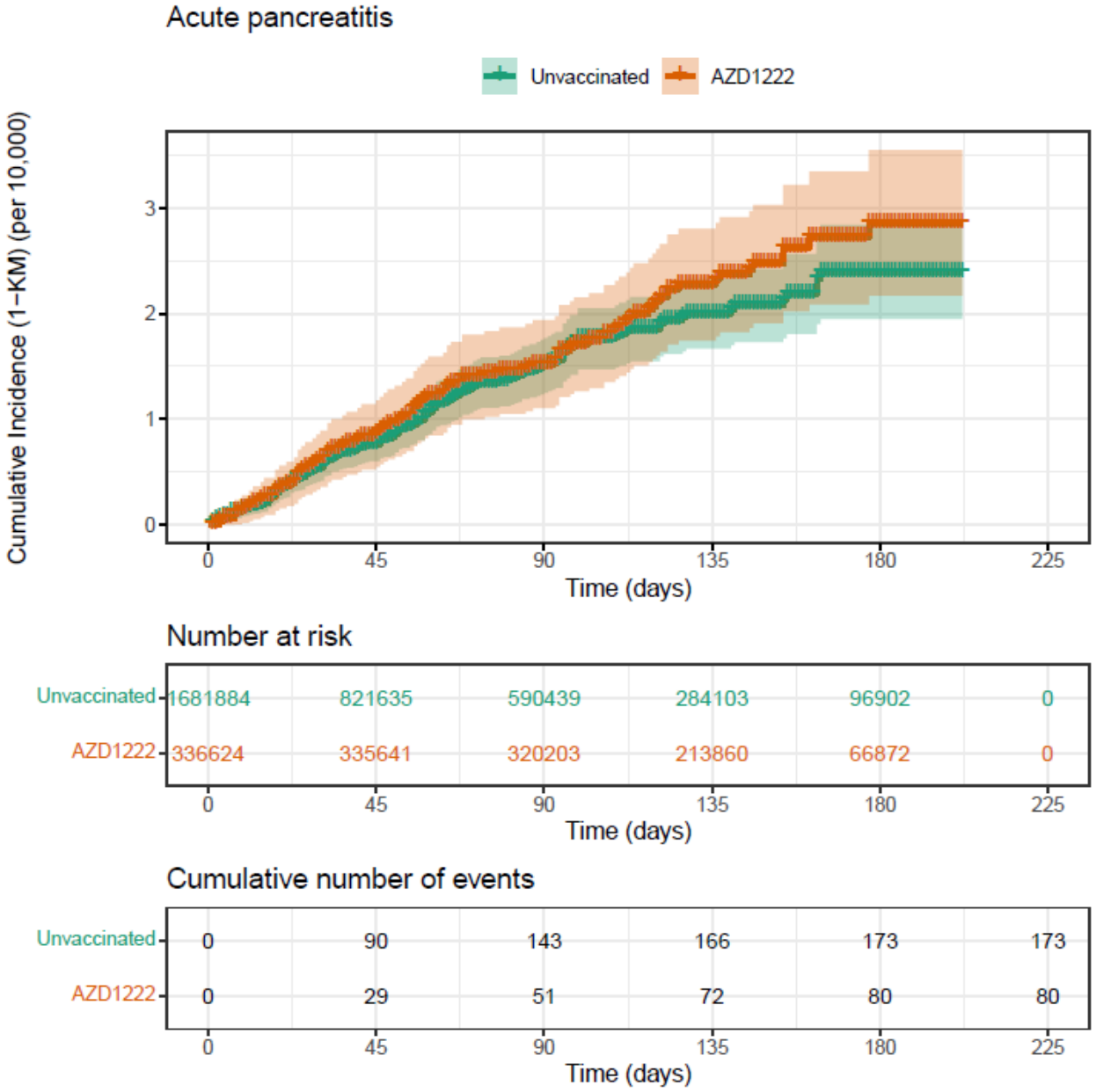


Figure 5.ARS. Multiple Sclerosis and Other Demyelinating Disorders, Cumulative Incidence With Unknown Risk Window

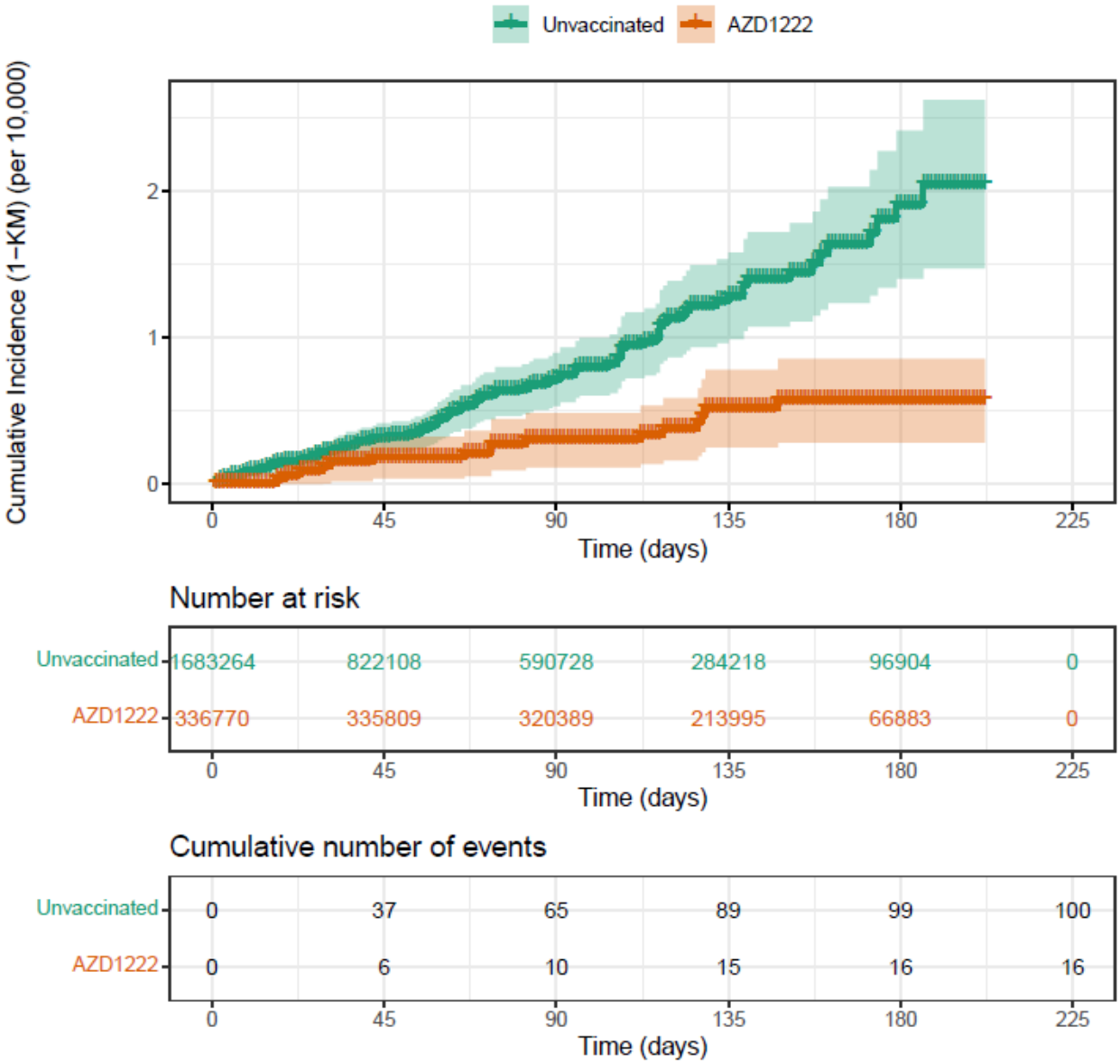


Figure 5.ARS. Type III Hypersensitivity Reactions, Cumulative Incidence With Unknown Risk Window

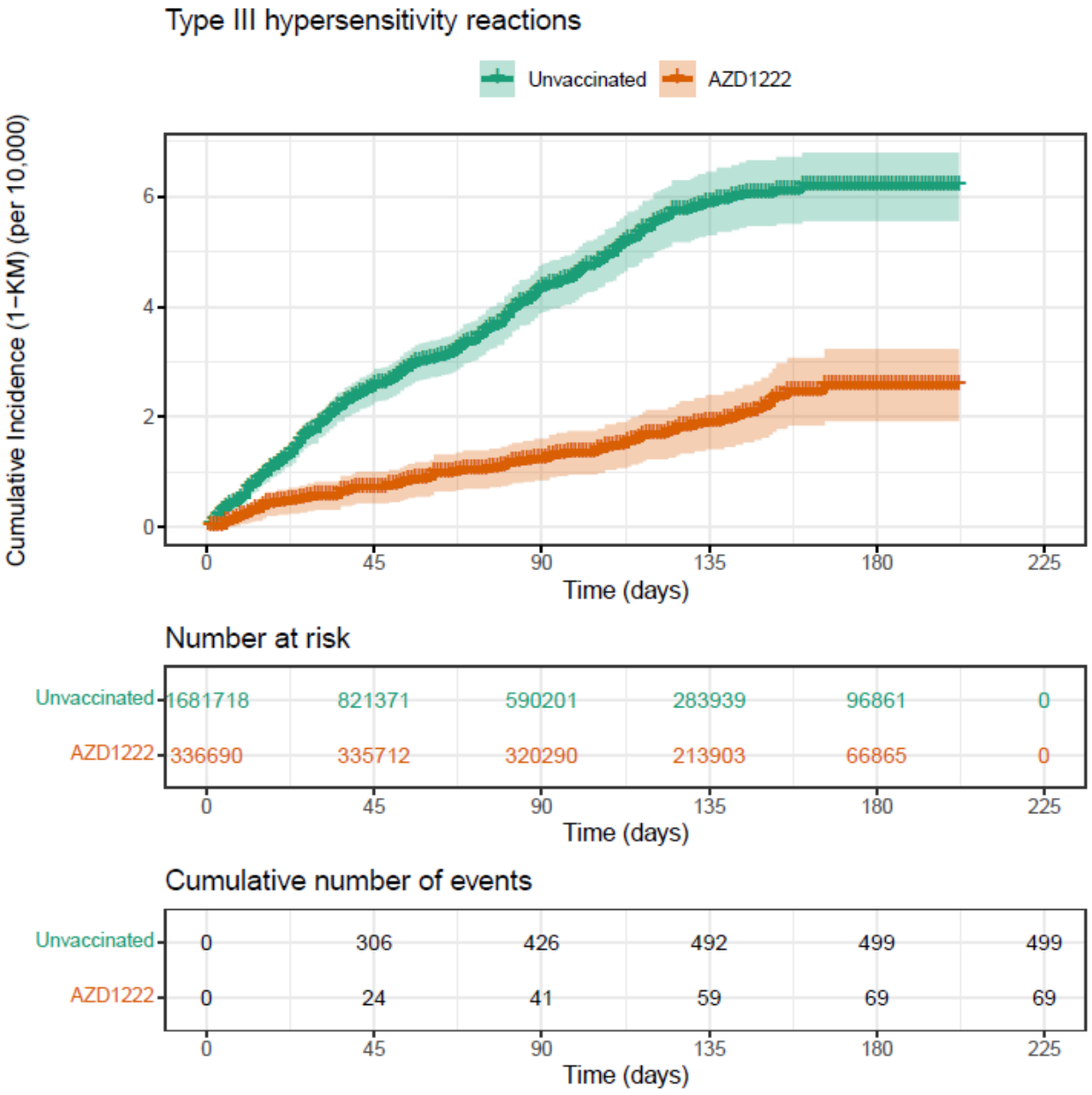


Figure 5.ARS. Vaccine-Associated Enhanced Disease, Including Vaccine-Associated Enhanced Respiratory Disease, Including ARDS, Cumulative Incidence With Unknown Risk Window

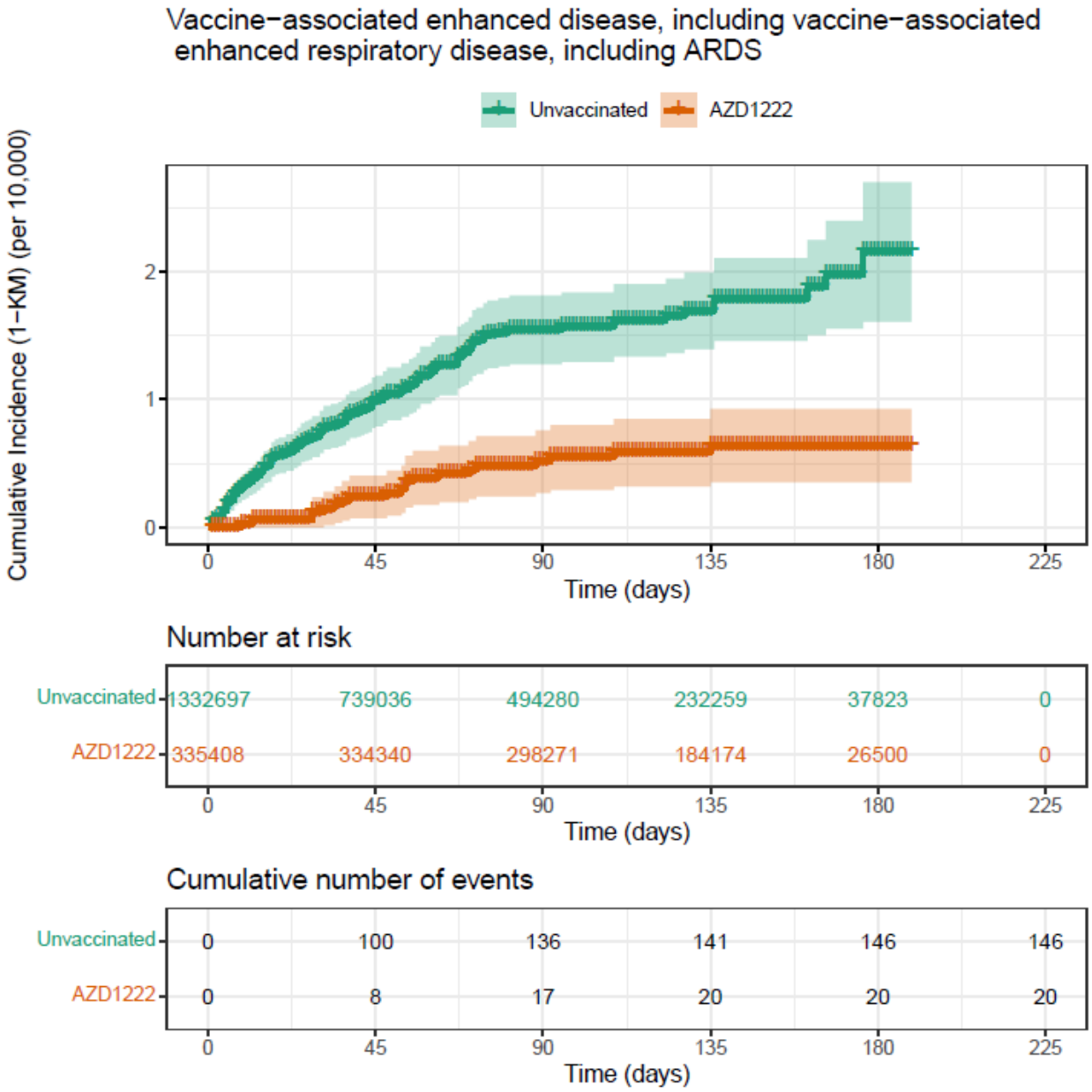


Figure 5.ARS. Erythema Multiforme, Cumulative Incidence With Unknown Risk Window

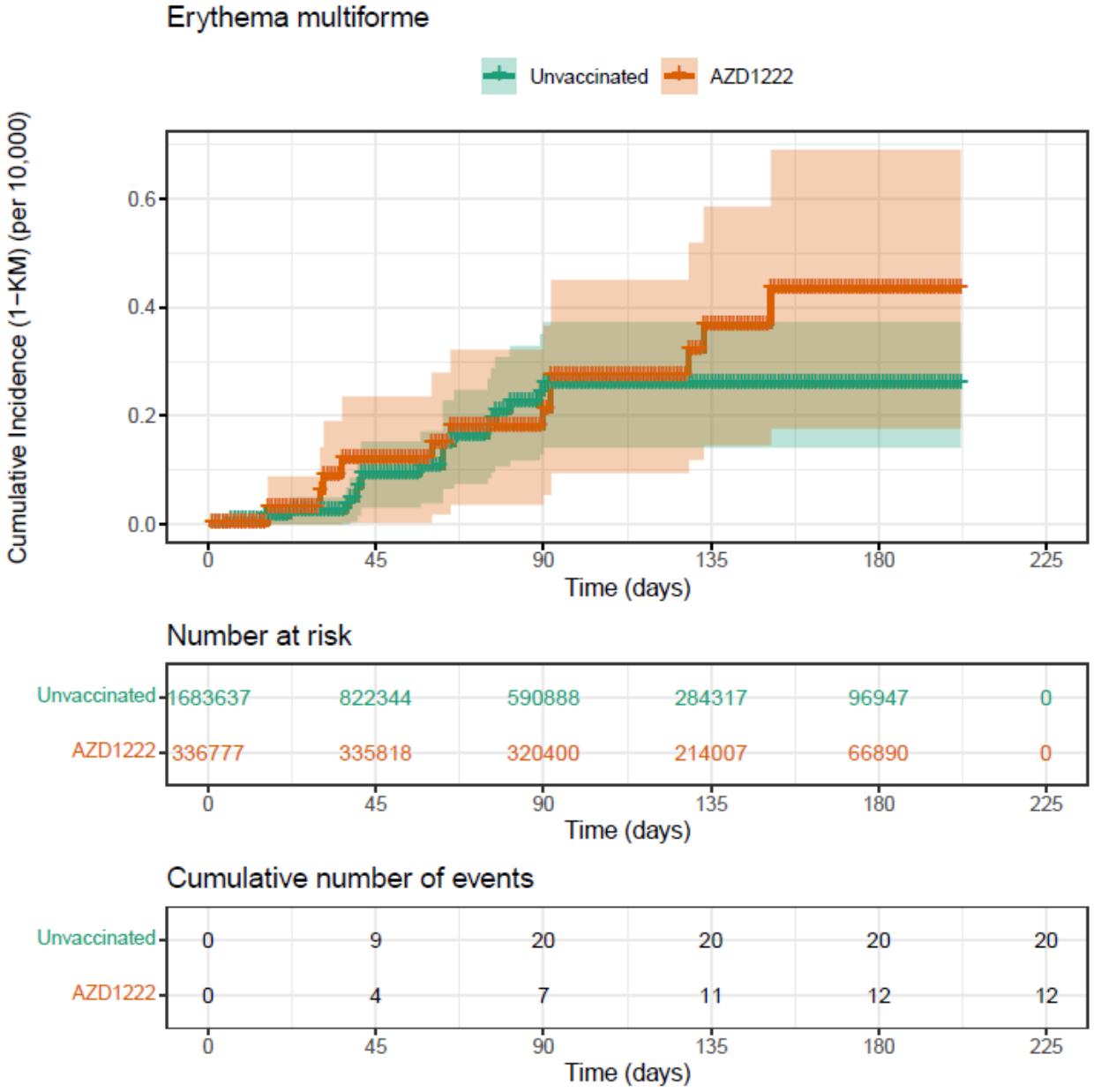
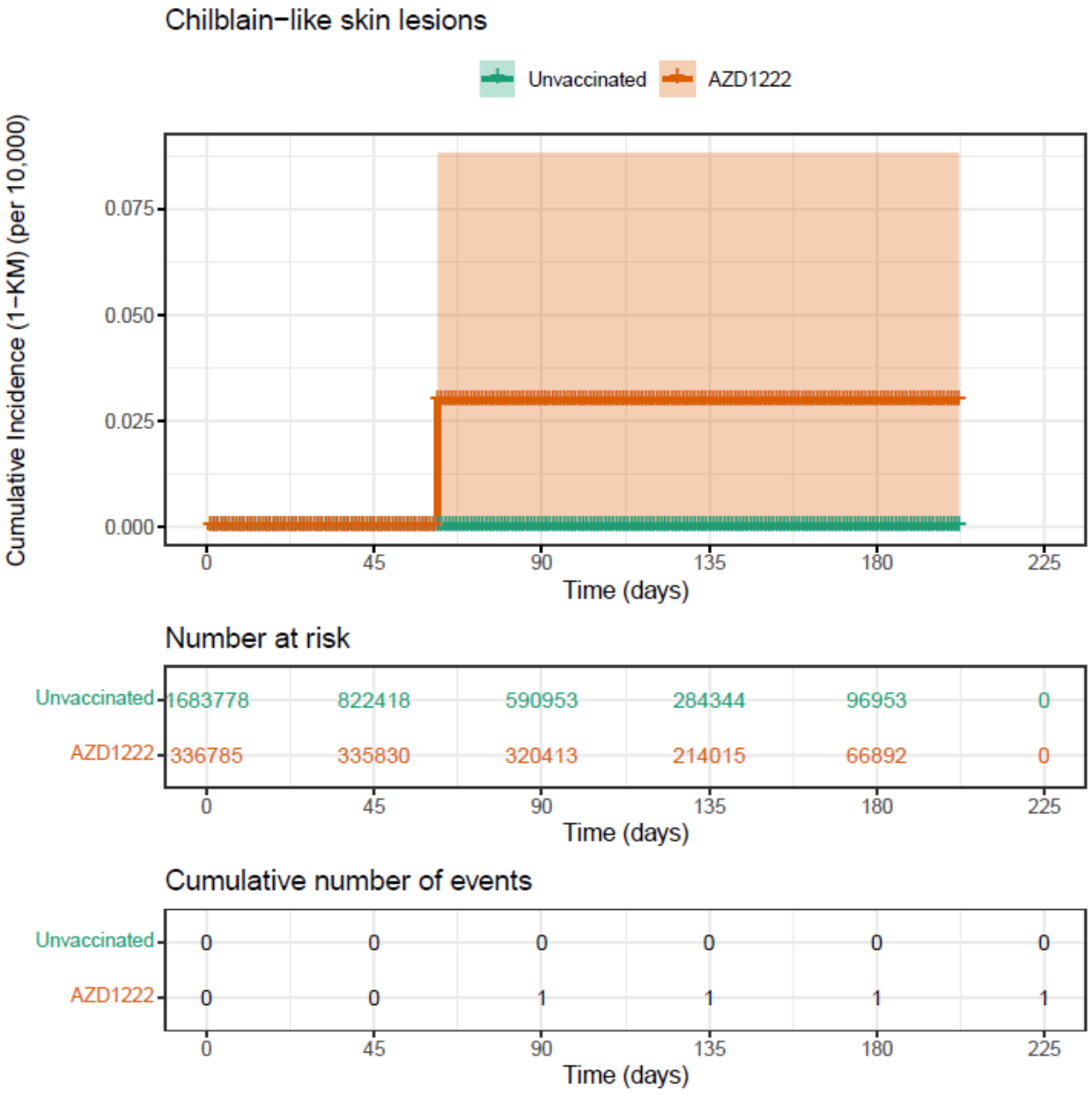


Figure 5.ARS. Chilblain-Like Skin Lesions, Cumulative Incidence With Unknown Risk Window



B 2.4 PHARMO, the Netherlands

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Table 1.1.PHARMO. Baseline Characteristics Among the *All Vaccinated Population*, AZD1222 Cohort

	Over all the study period included in interim report 1	
	N	%[a]
Total	168,229	100.00%
Calendar quarter at index date		
Q1 2021	39,864	23.70%
Q2 2021	128,365	76.30%
Q3 2021	0	0.00%
Q4 2021	0	0.00%
Q1 2022	0	0.00%
Q2 2022	0	0.00%
Duration of lookback period (years)		
Mean (SD)	10.89	(1.56)
Median (Q1, Q3)	11	(11,11)
Age at index date (years)		
Mean (SD)	59.81	(9.62)
Median (Q1, Q3)	62	(60,64)
Age groups (years)		
0-11	[redacted]	
12-15	[redacted]	
16-19	843	0.50%
20-29	4,181	2.49%
30-39	4,533	2.69%
40-49	6,965	4.14%
50-59	13,129	7.80%
60-69	133,799	79.53%
70-79	2,066	1.23%
80+	2,708	1.61%
Sex, female	87,284	51.88%
COVID-19 history (diagnosis or test)	20,794	12.36%

N, number; Q1, quartile 1; Q3, quartile 3; SD, standard deviation.
[a] Counts and percentages, unless otherwise specified.

Table 2.1.PHARMO. Incidence Rates or Prevalence Proportions of AESIs With Well-Defined Risk Window and Cumulative Incidence (1 − KM) of AESIs With Unknown Risk Window Among the *All Vaccinated Population*

		All AZD1222 vaccinated population				
AESI (risk window, days)	Risk esti-mator	N Subjects	N Out-comes	Person-years	Risk per 10,000	95% CI
Myasthenia gravis[a] (1-365)	1-KM	NA				
Thrombosis without thrombocytopenia[b] (1-42)	IR	166,908	0	20,769.8	0.00	(0.00-1.78)
Thrombosis with thrombocytopenia syndrome[b] (1-42)	IR	166,908	0	20,769.8	0.00	(0.00-1.78)
Narcolepsy[b] (1-42)	IR	166,908	0	20,769.8	0.00	(0.00-1.78)
Thrombocytopenia with associated bleeding[b] (1-42)	IR	166,908	0	20,769.8	0.00	(0.00-1.78)
Autoimmune thyroiditis[a] (1-180)	1-KM	166,906	[redacted]	[redacted]	0.08	(0.00-27.88)
Acute aseptic arthritis[b] (1-42)	IR	166,867	5	20,764.4	2.41	(0.78-5.62)
Guillain-Barré syndrome[b] (1-42)	IR	166,905	0	20,769.4	0.00	(0.00-1.78)
Thrombocytopenia[b] (1-42)	IR	166,886	5	20,766.7	2.41	(0.78-5.62)
Capillary leak syndrome[a] (1-365)	1-KM	NA				
Postural orthostatic tachycardia syndrome[b] (1-42)	IR	NA				
Acute cardiac injury including microangiopathy, cardiogenic shock, heart failure[b] (1-90)	IR	166,626	69	31,529.1	21.88	(17.03-27.70)
Stress cardiomyopathy[b] (1-42)	IR	166,906	0	20,769.6	0.00	(0.00-1.78)
Myocardial infarction[b] (1-28)	IR	166,822	6	14,648.0	4.10	(1.50-8.92)
Myocarditis/Pericarditis[b] (1-42)	IR	166,905	0	20,769.2	0.00	(0.00-1.78)
Acute pancreatitis[a] (1-365)	1-KM	166,905	[redacted]	[redacted]	0.15	(0.00-27.96)
Acute kidney injury[b] (1-14)	IR	166,273	35	7,641.5	45.80	(31.90-63.70)
Acute liver injury[b] (1-14)	IR	166,898	0	7,671.8	0.00	(0.00-4.81)
Multiple sclerosis, and other demyelinating disorders[a] (1-365)	1-KM	166,896	[redacted]	[redacted]	0.48	(0.00-28.29)
Transverse myelitis[b] (1-90)	IR	166,908	0	31,584.8	0.00	(0.00-1.17)
Encephalitis (including ADEM)[b] (1-42)	IR	166,898	[redacted]	[redacted]	1.93	(0.52-4.93)

AESI (risk window, days)	Risk esti-mator	All AZD1222 vaccinated population				
		N Subjects	N Out-comes	Person-years	Risk per 10,000	95% CI
Other peripheral and polyneuropathies[b] (1-42)	IR	NA				
Generalised convulsions[b] (0-14)	IR	168,179	[redacted]	[redacted]	1.21	(0.03-6.75)
Optic neuritis/neuromyelitis optica spectrum disorder[b] (1-42)	IR	NA				
Bell's palsy[b] (1-42)	IR	166,753	34	20,748.9	16.39	(11.35-22.90)
Fibromyalgia[a] (91-365)	1-KM	NA				
Chronic fatigue syndrome/ME/PVFS[a] (183-365)	1-KM	NA				
Anosmia, ageusia[a] (1-365)	1-KM	166,794	11	32,113.3	1.17	(0.00-28.99)
Type III hypersensitivity reactions[a] (1-365)	1-KM	NA				
Anaphylaxis[c] (0-2)	PP	167,629	39	1,731.5	2.33	(1.65-3.18)
Rhabdomyolysis[b] (1-42)	IR	166,908	[redacted]	[redacted]	0.96	(0.12-3.48)
Multisystem inflammatory syndrome in adults/children[b] (1-42)	IR	166,908	0	20,769.8	0.00	(0.00-1.78)
Sudden death[c] (0-6)	PP	168,188	[redacted]	[redacted]	0.18	(0.04-0.52)
Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease, including ARDS[a] (14-365)	1-KM	162,953	[redacted]	[redacted]	0.19	(0.00-33.83)
ARDS[b] (1-28)	IR	166,903	[redacted]	[redacted]	1.36	(0.17-4.93)
Erythema multiforme[a] (1-365)	1-KM	166,904	[redacted]	[redacted]	0.06	(0.00-27.87)
Chilblain-like skin lesions[a] (1-365)	1-KM	166,826	[redacted]	[redacted]	0.19	(0.00-28.00)

ADEM, acute disseminated encephalomyelitis; AESI, adverse event of special interest; ARDS, acute respiratory distress syndrome; CI, confidence interval; IR, incidence rate; KM, Kaplan-Meier; ME, myalgic encephalitis; N, number; NA, not available; PR, prevalence rate; PVFS, postviral fatigue syndrome; PY, person-years.

[a] Cumulative incidence (1-KM) per 10,000, for these outcomes with unknown risk windows.

[b] Incidence rate (IR) per 10,000 person-years, for outcomes with well-defined risk windows.

[c] Prevalence proportion (PP) per 10,000, for outcomes with well-defined and very short risk windows.

Table 2. PHARMO. TTS. Cumulative Incidence (1 − KM) of Thrombosis With Thrombocytopenia Syndrome Among the *All Vaccinated Population*, by Age Groups and Sex

	All AZD1222 vaccinated population				
	N Subjects	N Out-comes	Person-years	1-KM per 10,000	95% CI
By age groups (years)					
0-11	[redacted]	[redacted]	[redacted]	0.00	(0.00-4282.78)
12-15	[redacted]	[redacted]	[redacted]	0.00	(0.00-5245.32)
16-19	839	0	101.0	0.00	(0.00-419.53)
20-29	4,159	0	499.1	0.00	(0.00-210.39)
30-39	4,504	0	546.9	0.00	(0.00-202.17)
40-49	6,915	0	870.2	0.00	(0.00-163.23)
50-59	13,045	0	1,646.8	0.00	(0.00-118.91)
60-69	132,701	0	16,597.1	0.00	(0.00-37.28)
70-79	2,052	0	227.7	0.00	(0.00-291.64)
80+	2,688	0	280.4	0.00	(0.00-214.54)
By sex					
Male	80,280	0	9,990.2	0.00	(0.00-47.93)
Female	86,625	0	10,779.1	0.00	(0.00-46.14)

CI, confidence interval; KM, Kaplan-Meier; N, number; PY, person-years.
[a] Numbers correspond to counts and percentages unless otherwise specified.

Table 3.1.PHARMO. Description of the Utilisation Pattern of Subsequent Doses of a COVID-19 Vaccine in the *All Vaccinated First Dose Population*, Over All the Study Period

AZD1222 cohort	Over all the study period included in interim report 1[a]	
	N	%
Subjects with a first dose of AZD1222 (Vaxzevria)	168,229	
Subjects who had received only a first dose of AZD1222 at the end of study period for interim report 1	121,536	72.24%
Subjects with a first dose of AZD122 who receive a second dose of any COVID-19 vaccine and time between doses	46,693	27.76%
Vaxzevria (COVID-19 Vaccine AstraZeneca)	46,693	27.76%
Time between dose 1 and dose 2, weeks		
Mean (SD)	11.31	(1.09)
Median (Q1-Q3)	11.0	(10.7, 12.0)
min, max	10	21
<2 weeks	0	0.00%
2-4 weeks	0	0.00%
5-8 weeks	0	0.00%
9-12 weeks	41,923	89.78%
13-18 weeks	4,761	10.20%
>18 weeks	9	0.02%
Comirnaty (COVID-19 Vaccine Pfizer-BioNTech)	0	0.00%
Time between dose 1 and dose 2, weeks		
Mean (SD)		
Median (Q1-Q3)		
min, max		
<2 weeks	0	0.00%
2-4 weeks	0	0.00%
5-8 weeks	0	0.00%
9-12 weeks	0	0.00%
13-18 weeks	0	0.00%
>18 weeks	0	0.00%

AZD1222 cohort	Over all the study period included in interim report 1[a]	
	N	%
Spikevax (COVID-19 Vaccine Moderna)	0	0.00%
Time between dose 1 and dose 2, weeks		
Mean (SD)		
Median (Q1-Q3)		
min, max		
<2 weeks	0	0.00%
2-4 weeks	0	0.00%
5-8 weeks	0	0.00%
9-12 weeks	0	0.00%
13-18 weeks	0	0.00%
>18 weeks	0	0.00%
COVID-19 Vaccine Janssen	0	0.00%
Time between dose 1 and dose 2, weeks		
Mean (SD)		
Median (Q1-Q3)		
min, max		
<2 weeks	0	0.00%
2-4 weeks	0	0.00%
5-8 weeks	0	0.00%
9-12 weeks	0	0.00%
13-18 weeks	0	0.00%
>18 weeks	0	0.00%
Other COVID-19 vaccines	0	0.00%
Time between dose 1 and dose 2, weeks		
Mean (SD)		
Median (Q1-Q3)		
min, max		
<2 weeks	0	0.00%
2-4 weeks	0	0.00%
5-8 weeks	0	0.00%
9-12 weeks	0	0.00%
13-18 weeks	0	0.00%
>18 weeks	0	0.00%

AZD1222 cohort	Over all the study period included in interim report 1[a]	
	N	%
Subjects with a first and second dose of AZD122 who receive a third dose of any COVID-19 vaccine and time between doses	0	0.00%
Vaxzevria (COVID-19 Vaccine AstraZeneca)	0	0.00%
Time between dose 2 and dose 3		
Mean (SD)		
Median (Q1-Q3)		
min, max		
<12 weeks	0	0.00%
12-24 weeks	0	0.00%
25-37 weeks	0	0.00%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%
Comirnaty (COVID-19 Vaccine Pfizer-BioNTech)	0	0.00%
Time between dose 2 and dose 3		
Mean (SD)		
Median (Q1-Q3)		
min, max		
<12 weeks	0	0.00%
12-24 weeks	0	0.00%
25-37 weeks	0	0.00%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%
Spikevax (COVID-19 Vaccine Moderna)	0	0.00%
Time between dose 2 and dose 3		
Mean (SD)		
Median (Q1-Q3)		
min, max		
<12 weeks	0	0.00%
12-24 weeks	0	0.00%
25-37 weeks	0	0.00%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%

AZD1222 cohort	Over all the study period included in interim report 1[a]	
	N	%
COVID-19 Vaccine Janssen	0	0.00%
Time between dose 2 and dose 3		
Mean (SD)		
Median (Q1-Q3)		
min, max		
<12 weeks	0	0.00%
12-24 weeks	0	0.00%
25-37 weeks	0	0.00%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%
Other COVID-19 vaccines	0	0.00%
Time between dose 2 and dose 3		
Mean (SD)		
Median (Q1-Q3)		
min, max		
<12 weeks	0	0.00%
12-24 weeks	0	0.00%
25-37 weeks	0	0.00%
38-50 weeks	0	0.00%
>50 weeks	0	0.00%

Q1 = Quartile 1; Q3 = Quartile 3; SD = Standard deviation

Table 4.PHARMO. Cohort Attrition for the *Matched Population*

Cohort	N	(%)
AZD1222 cohort		
All vaccinated population	168,229	
All vaccinated first dose population	168,229	(100.00%)
And with at least 12 months lookback period (eligible to be matched)	168,042	(99.89%)
Unique vaccinated subjects not matched	955	(0.57%)
Unique vaccinated subjects matched	167,087	(99.43%)
Matching ratio 1:1	1,340	(0.80%)
Matching ratio 1:2	1,565	(0.94%)
Matching ratio 1:3	1,615	(0.97%)
Matching ratio 1:4	1,663	(1.00%)
Matching ratio 1:5	160,904	(96.30%)
Unvaccinated cohort		
Unique subjects with no record of vaccination with any COVID-19 vaccine during the study period	2,506,899	
And with at least 12 months lookback period (eligible to be matched)	2,501,869	(99.80%)
Unique unvaccinated subjects matched	323,940	(12.95%)
Unique unvaccinated subjects not matched	2,177,929	(87.05%)
Non-unique unvaccinated subjects matched	820,487	
Number of times an unvaccinated subject was matched		
Median (Q1-Q3)	1	(1-3)
Min-Max		1-72
1	175,278	(54.11%)
2	50,821	(15.69%)
3	29,804	(9.20%)
4	20,432	(6.31%)
5 or more	47,605	(14.70%)

N = number; Q1 = Quartile 1; Q3 = Quartile 3

Table 5.PHARMO. Reasons for Censoring Follow-up Among the *Matched Population* Cohorts

	AZD1222 cohort		Unvaccinated cohort	
Cohort design	**N**	**(%)**	**N**	**(%)**
Total	167,087	(100.00%)	820,487	(100.00%)
Person-months of follow-up				
Mean follow-up (SD), months	2.29	(1.03)	1.54	(1.04)
Median follow-up (Q1-Q3), months	2.3	(1.6,2.8)	1.4	(0.7,2.3)
P1 - P99 follow-up, months	<0.1	-4.2	<0.1	-4.1
Received AZD1222, n (%)	0	(0.00%)	166,234	(20.26%)
Received any COVID-19 vaccine other than AZD1222, n (%)	0	(0.00%)	256,856	(31.31%)
Censored 365 days after the second dose of AZD1222, n (%)	0	(0.00%)	0	(0.00%)
End of study period, n (%)	163,112	(97.62%)	375,312	(45.74%)
Enrolment termination date in the health plan or system, n(%)	3,830	(2.29%)	21,351	(2.60%)
Death, n(%)	145	(0.09%)	734	(0.09%)

N = number; Q1 = Quartile 1; Q3 = Quartile 3

Table 11.1.PHARMO. Crude Risk Estimates for AESIs in the *Matched Cohorts* Based on Definition and Duration of Risk Windows

		AZD1222 cohort					Unvaccinated cohort				
AESI (risk window, days)	**Risk esti-mator**	**N Patients**	**N Out-comes**	**Person-years**	**Risk per 10,000**	**95% CI**	**N Patients**	**N Out-comes**	**Person-years**	**Risk per 10,000**	**95% CI**
Myasthenia gravis[a] (1-365)	1-KM	NA					NA				
Thrombosis without thrombocytopenia[b] (1-42)	IR	165,823	0	20,654.2	0.00	(0.00-1.79)	814,390	0	74,889.7		NR
Thrombosis with thrombocytopenia syndrome[b] (1-42)	IR	165,823	0	20,654.2	0.00	(0.00-1.79)	814,392	0	74,889.9		NR
Narcolepsy[b] (1-42)	IR	165,823	0	20,654.2	0.00	(0.00-1.79)	814,389	0	74,889.6		NR
Thrombocytopenia with associated bleeding[b] (1-42)	IR	165,823	0	20,654.2	0.00	(0.00-1.79)	814,392	0	74,889.9		NR
Autoimmune thyroiditis[a] (1-180)	1-KM	165,821	[redacted]	[redacted]	0.08	(0.00-27.98)	814,372	0	105,300.7	0.00	(0.00-11.41)
Acute aseptic arthritis[b] (1-42)	IR	165,780	5	20,648.6	2.42	(0.79-5.65)	813,932	27	74,849.7	3.61	(1.74-7.48)
Guillain-Barré syndrome[b] (1-42)	IR	165,820	0	20,653.8	0.00	(0.00-1.79)	814,363	[redacted]	[redacted]	0.40	(0.06-2.84)
Thrombocytopenia[b] (1-42)	IR	165,801	5	20,651.1	2.42	(0.79-5.65)	814,188	13	74,872.6	1.74	(0.66-4.56)
Capillary leak syndrome[a] (1-365)	1-KM	NA					NA				
Postural orthostatic tachycardia syndrome[b] (1-42)	IR	NA					NA				

AESI (risk window, days)	Risk esti-mator	AZD1222 cohort					Unvaccinated cohort				
		N Patients	N Out-comes	Person-years	Risk per 10,000	95% CI	N Patients	N Out-comes	Person-years	Risk per 10,000	95% CI
Acute cardiac injury including microangiopathy, cardiogenic shock, heart failure[b] (1-90)	IR	165,542	66	31,353.1	21.05	(16.28-26.78)	812,167	181	103,868.0	17.43	(12.04-25.23)
Stress cardiomyopathy[b] (1-42)	IR	165,821	0	20,653.9	0.00	(0.00-1.79)	814,378	[redacted]	[redacted]	0.13	(0.02-0.95)
Myocardial infarction[b] (1-28)	IR	165,737	6	14,566.8	4.12	(1.51-8.97)	813,652	52	55,568.1	9.36	(2.54-34.46)
Myocarditis/Pericarditis[b] (1-42)	IR	165,820	0	20,653.6	0.00	(0.00-1.79)	814,380	[redacted]	[redacted]	0.13	(0.02-0.95)
Acute pancreatitis[a] (1-365)	1-KM	165,820	[redacted]	[redacted]	0.15	(0.00-28.05)	814,353	8	105,296.5	0.10	(0.00-11.51)
Acute kidney injury[b] (1-14)	IR	165,189	35	7,598.5	46.06	(32.08-64.06)	808,330	96	30,648.7	31.32	(22.34-43.92)
Acute liver injury[b] (1-14)	IR	165,813	0	7,628.8	0.00	(0.00-4.84)	814,309	[redacted]	[redacted]	0.32	(0.05-2.30)
Multiple sclerosis, and other demyelinating disorders[a] (1-365)	1-KM	165,811	[redacted]	[redacted]	0.48	(0.00-28.38)	814,302	10	105,290.1	0.15	(0.00-11.56)
Transverse myelitis[b] (1-90)	IR	165,823	0	31,408.5	0.00	(0.00-1.17)	814,389	0	104,145.5		NR
Encephalitis (including ADEM)[b] (1-42)	IR	165,813	[redacted]	[redacted]	1.94	(0.53-4.96)	814,288	[redacted]	[redacted]	0.13	(0.02-0.95)
Other peripheral and polyneuropathies[b] (1-42)	IR	NA					NA				

AESI (risk window, days)	Risk esti-mator	AZD1222 cohort					Unvaccinated cohort				
		N Patients	N Out-comes	Person-years	Risk per 10,000	95% CI	N Patients	N Out-comes	Person-years	Risk per 10,000	95% CI
Generalised convulsions[b] (0-14)	IR	167,054	[redacted]	[redacted]	1.22	(0.03-6.78)	820,108	[redacted]	[redacted]	0.89	(0.29-2.77)
Optic neuritis/neuromyelitis optica spectrum disorder[b] (1-42)	IR	NA					NA				
Bell's palsy[b] (1-42)	IR	165,670	34	20,633.5	16.48	(11.41-23.03)	812,845	132	74,746.1	17.66	(12.02-25.94)
Fibromyalgia[a] (91-365)	1-KM	NA					NA				
Chronic fatigue syndrome/ME/PVFS[a] (183-365)	1-KM	NA					NA				
Anosmia, ageusia[a] (1-365)	1-KM	165,710	11	31,934.9	1.18	(0.00-29.09)	813,395	62	105,169.2	1.59	(0.00-13.02)
Type III hypersensitivity reactions[a] (1-365)	1-KM	NA					NA				
Anaphylaxis[c] (0-2)	PP	166,502	39	1,721.0	2.34	(1.67-3.20)	815,033	86	7,372.8	1.06	(0.84-1.30)
Rhabdomyolysis[b] (1-42)	IR	165,823	[redacted]	[redacted]	0.97	(0.12-3.50)	814,389	0	74,889.5		NR
Multisystem inflammatory syndrome in adults/children[b] (1-42)	IR	165,823	0	20,654.2	0.00	(0.00-1.79)	814,392	0	74,889.9		NR
Sudden death[c] (0-6)	PP	167,062	[redacted]	[redacted]	0.18	(0.04-0.52)	820,287	48	16,686.9	0.59	(0.43-0.78)

AESI (risk window, days)	Risk esti-mator	AZD1222 cohort					Unvaccinated cohort				
		N Patients	N Out-comes	Person-years	Risk per 10,000	95% CI	N Patients	N Out-comes	Person-years	Risk per 10,000	95% CI
Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease, including ARDS[a] (14-365)	1-KM	160,581	[redacted]	[redacted]	0.19	(0.00-34.08)	675,409	[redacted]	[redacted]	0.04	(0.00-16.57)
ARDS[b] (1-28)	IR	165,817	[redacted]	[redacted]	1.37	(0.17-4.96)	814,316	[redacted]	[redacted]	0.18	(0.03-1.28)
Erythema multiforme[a] (1-365)	1-KM	165,819	[redacted]	[redacted]	0.06	(0.00-27.96)	814,362	0	105,298.7	0.00	(0.00-11.41)
Chilblain-like skin lesions[a] (1-365)	1-KM	165,740	[redacted]	[redacted]	0.19	(0.00-28.09)	813,567	20	105,195.8	0.37	(0.00-11.79)

ADEM, acute disseminated encephalomyelitis; AESI, adverse event of special interest; ARDS, acute respiratory distress syndrome; CI, confidence interval; IR, incidence rate; KM, Kaplan-Meier; ME, myalgic encephalitis; N, number; NA, not available; NR, not reportable; PR, prevalence rate; PVFS, postviral fatigue syndrome; PY, person-years.

[a] Cumulative incidence (1-KM) per 10,000, for these outcomes with unknown risk windows.

[b] Incidence rate (IR) per 10,000 person-years, for outcomes with well-defined risk windows.

[c] Prevalence proportion (PP) per 10,000, for outcomes with well-defined and very short risk windows.

Figure1.PHARMO. Number of Subjects Vaccinated With a First Dose of AZD1222 Who Were Excluded, Included, and Could Be Matched by Calendar Time

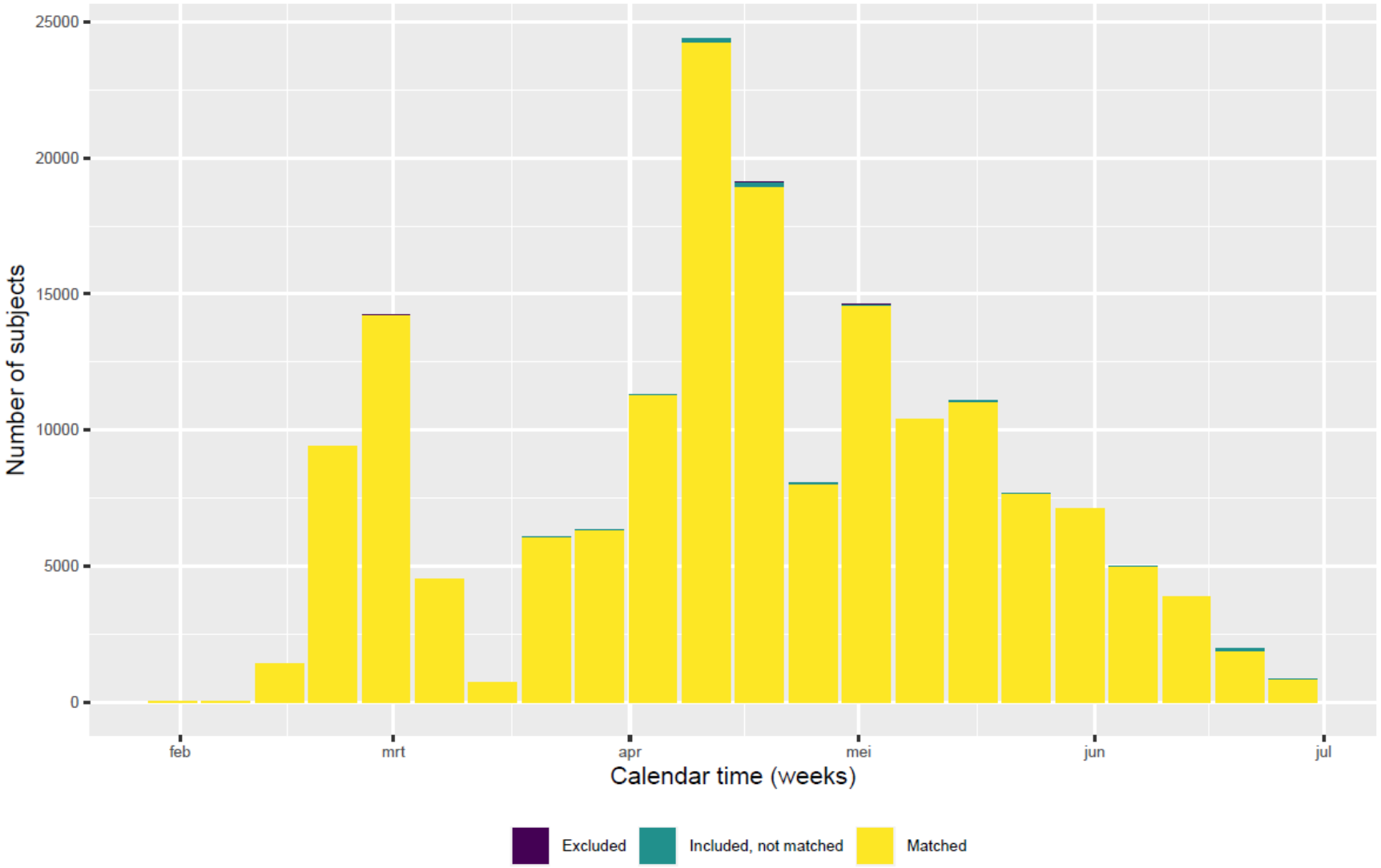


Figure2.PHARMO. AZD1222 Cohort, Reasons for Censoring Follow-up, by Quarter

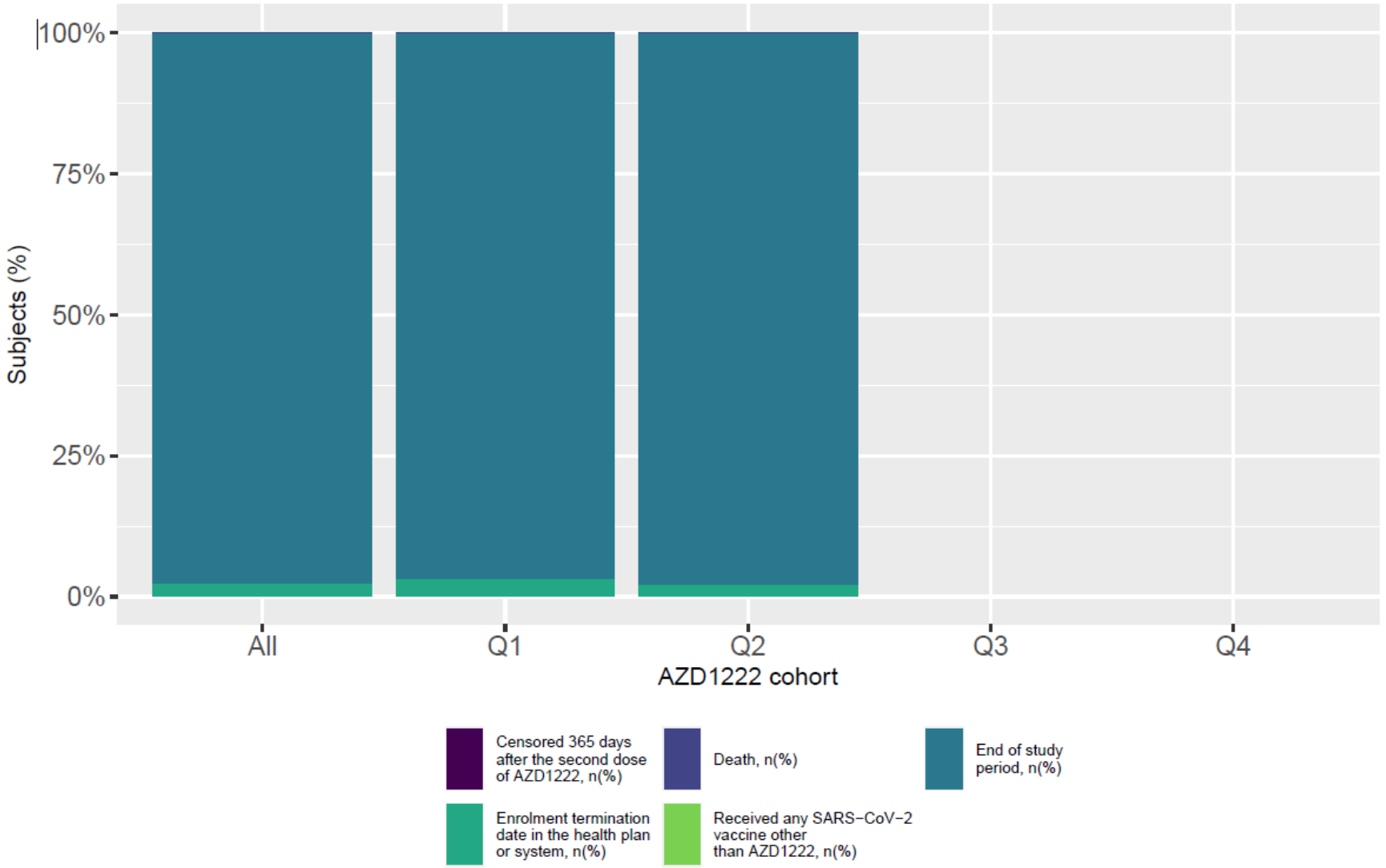


Figure2.PHARMO. Unvaccinated Cohort, Reasons for Censoring Follow-up, by Quarter

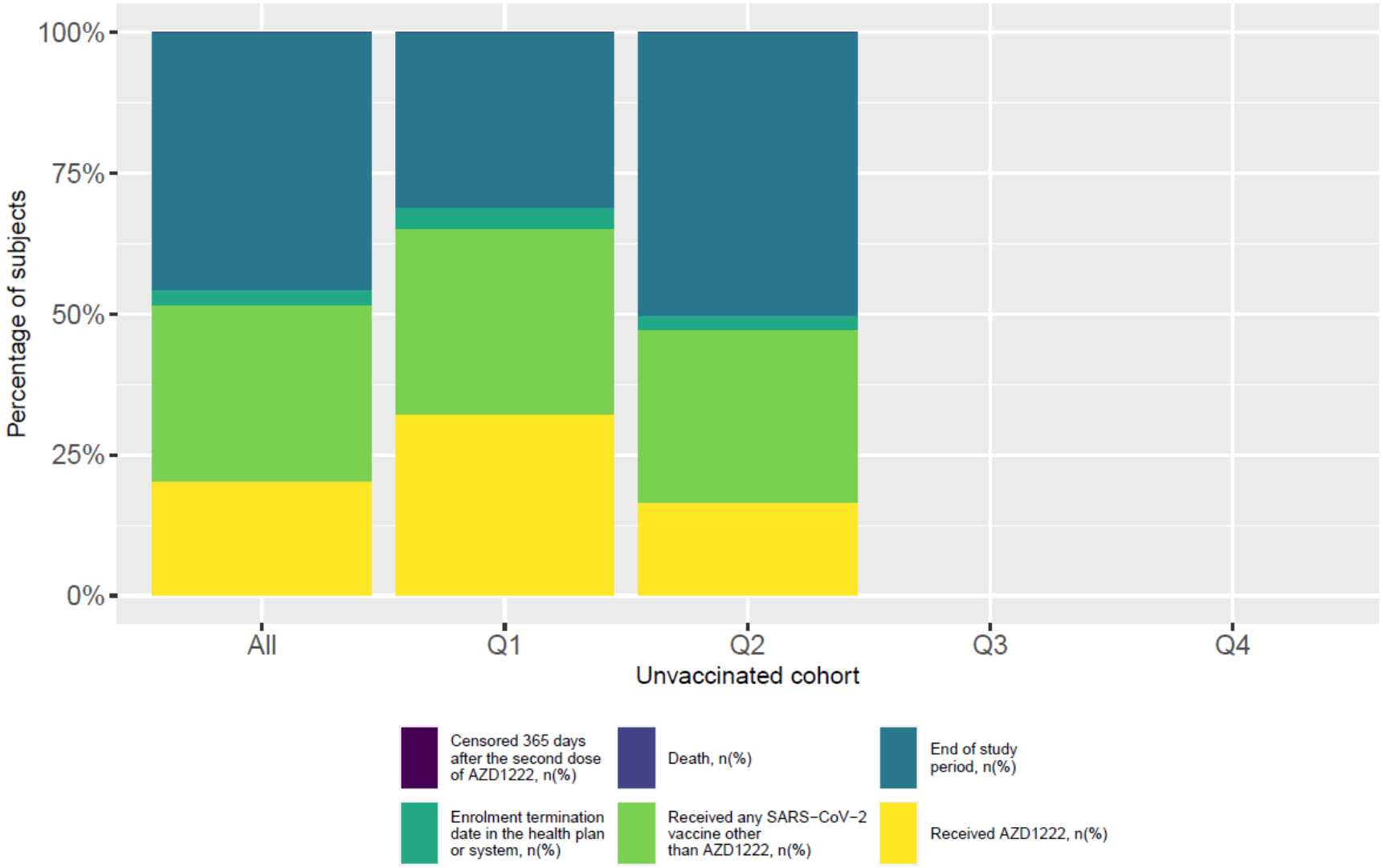


Figure 5.PHARMO. Autoimmune Thyroiditis, Cumulative Incidence With Unknown Risk Window

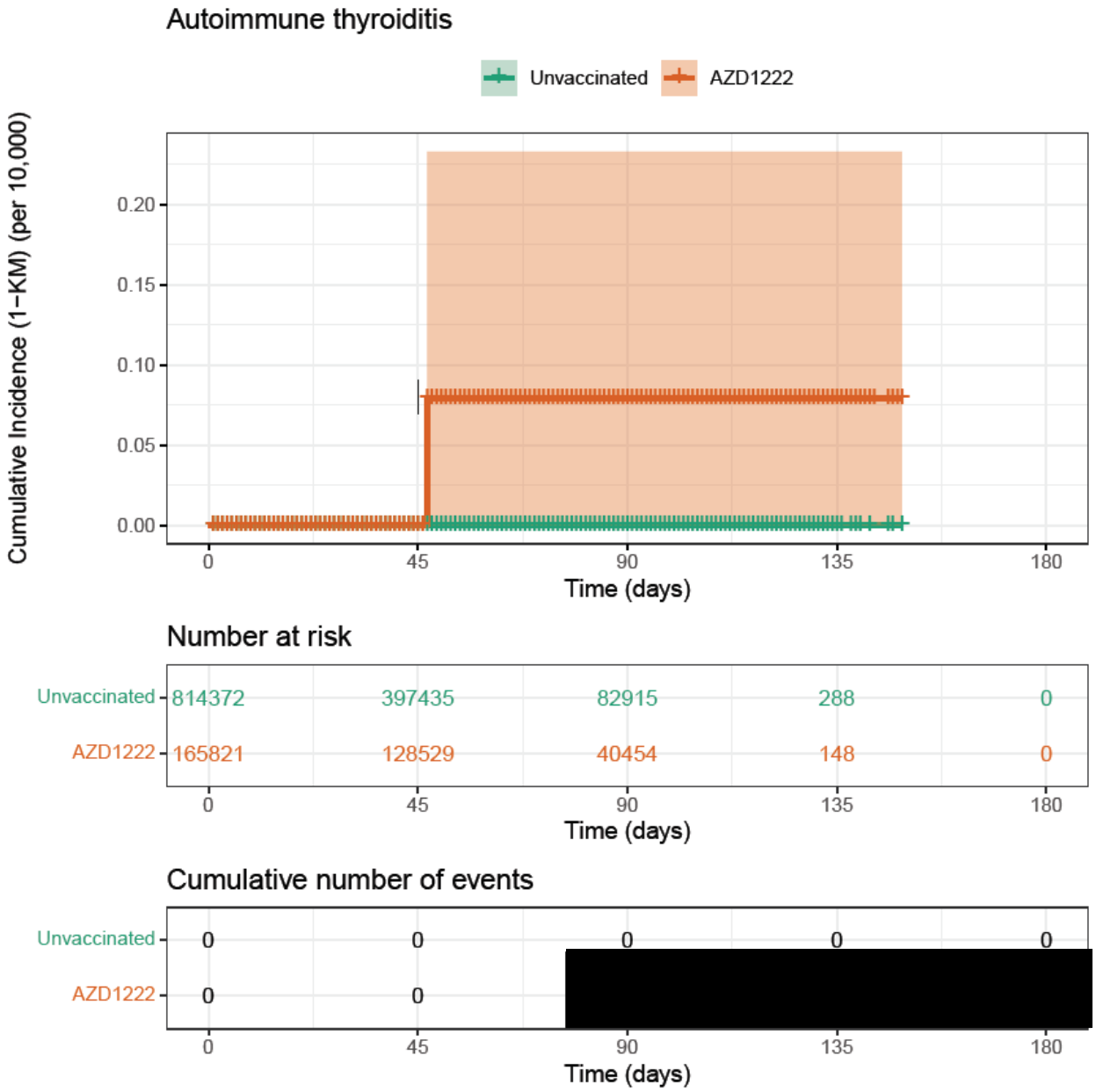


Figure 5.PHARMO. Acute Pancreatitis, Cumulative Incidence With Unknown Risk Window

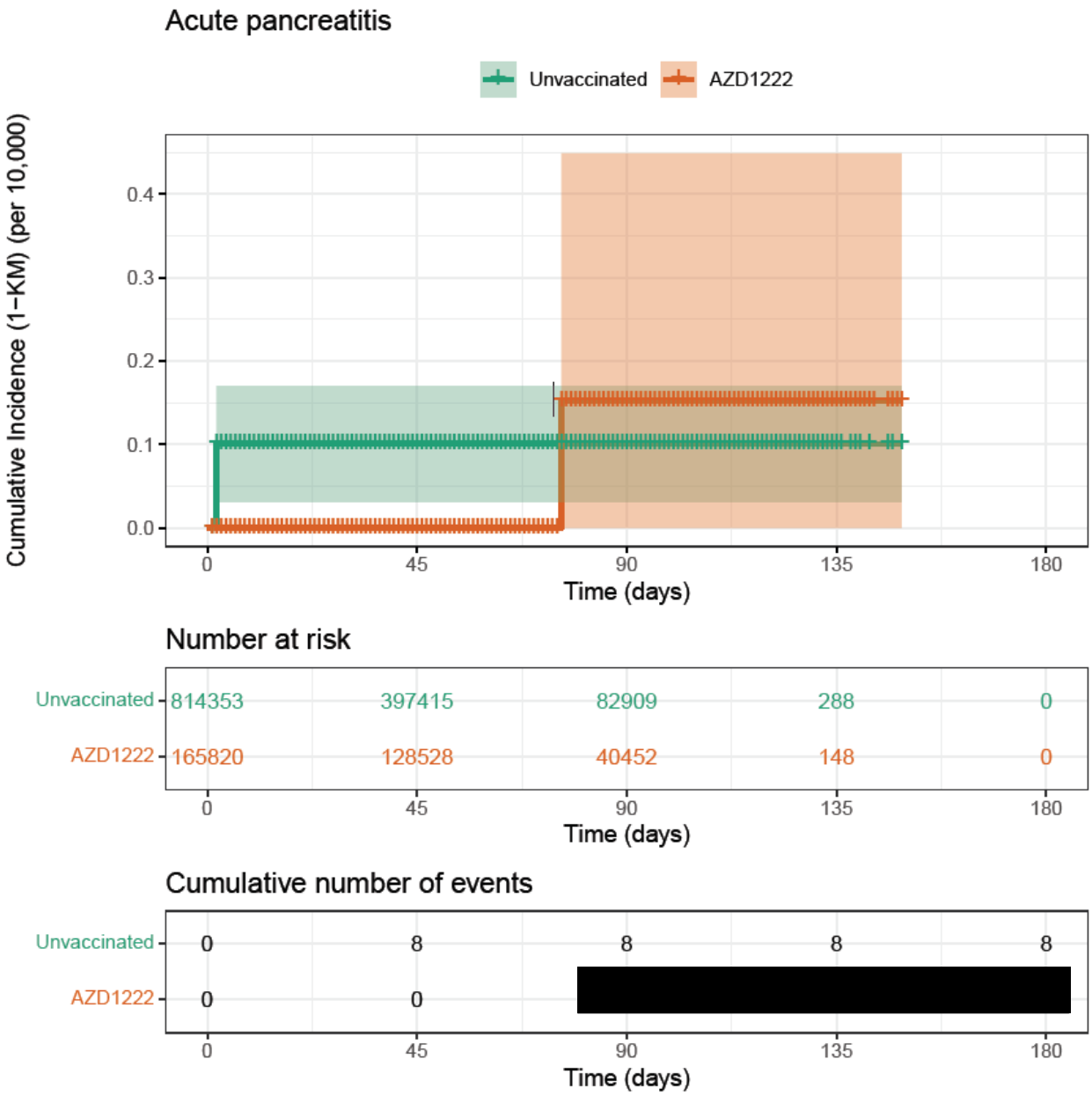


Figure 5.PHARMO. Multiple Sclerosis and Other Demyelinating Disorders, Cumulative Incidence With Unknown Risk Window

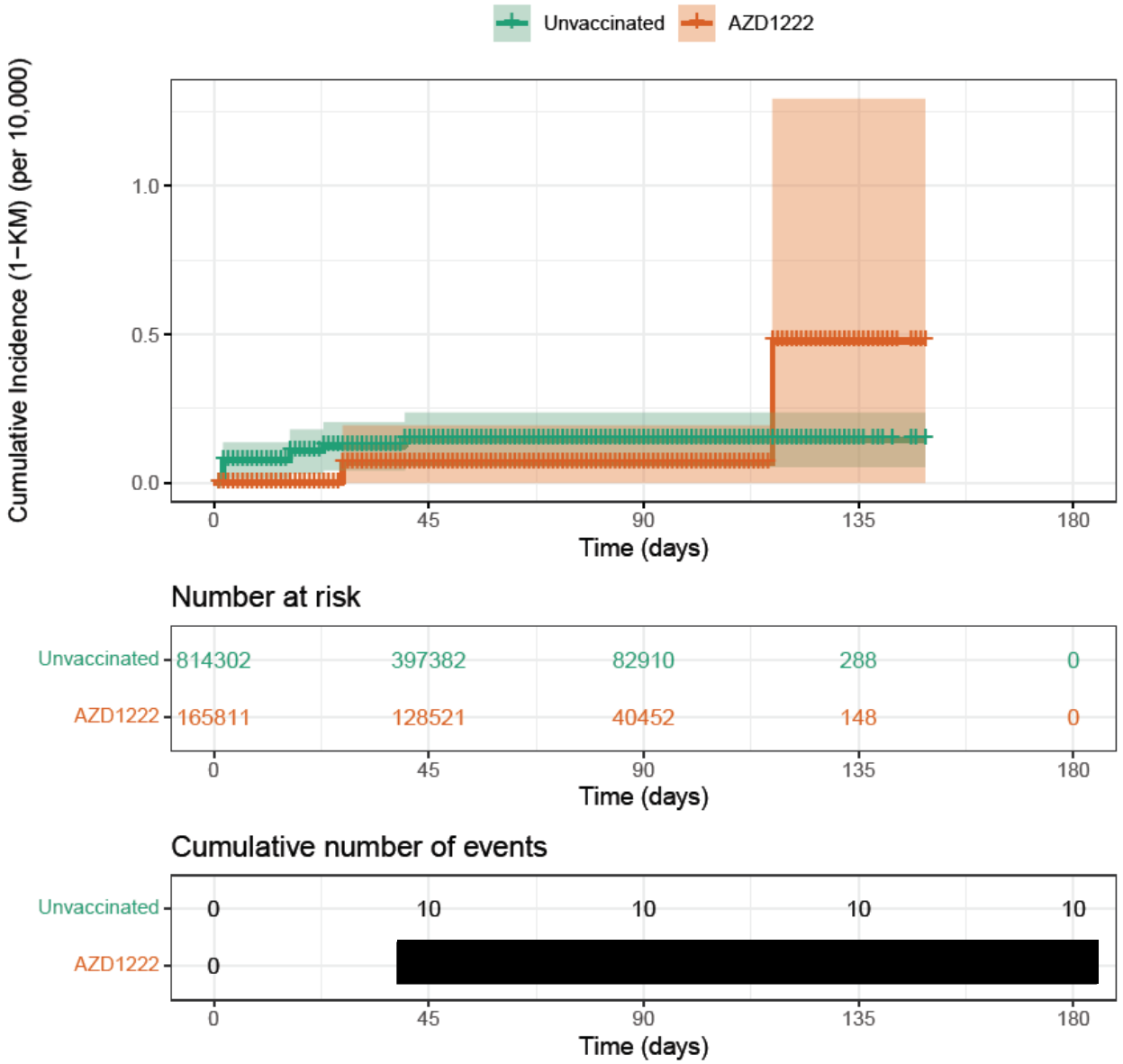


Figure 5.PHARMO. Anosmia, Ageusia, Cumulative Incidence With Unknown Risk Window

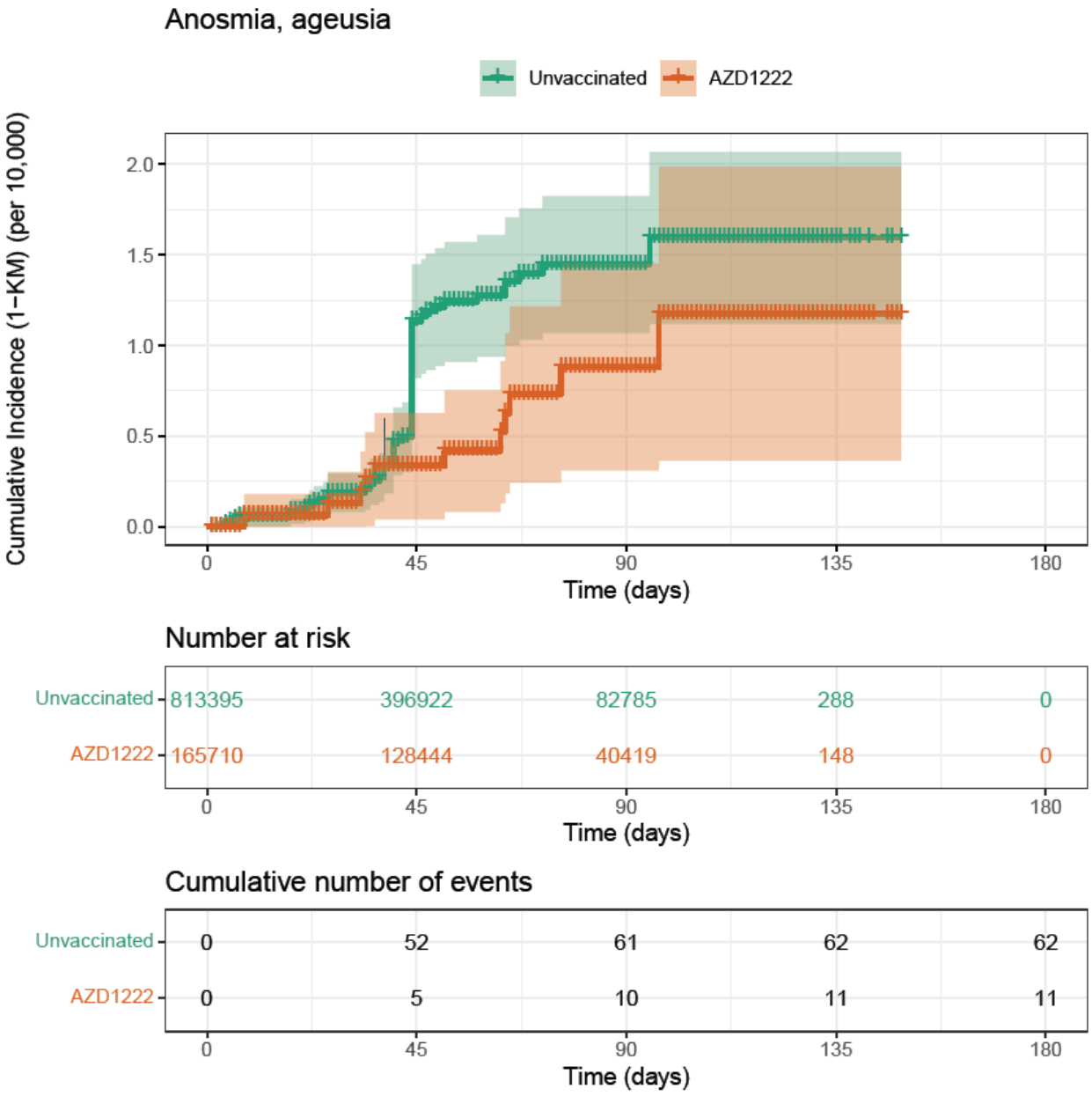


Figure 5.PHARMO. Vaccine-Associated Enhanced Disease, Including Vaccine-Associated Enhanced Respiratory Disease, Including ARDS, Cumulative Incidence With Unknown Risk Window

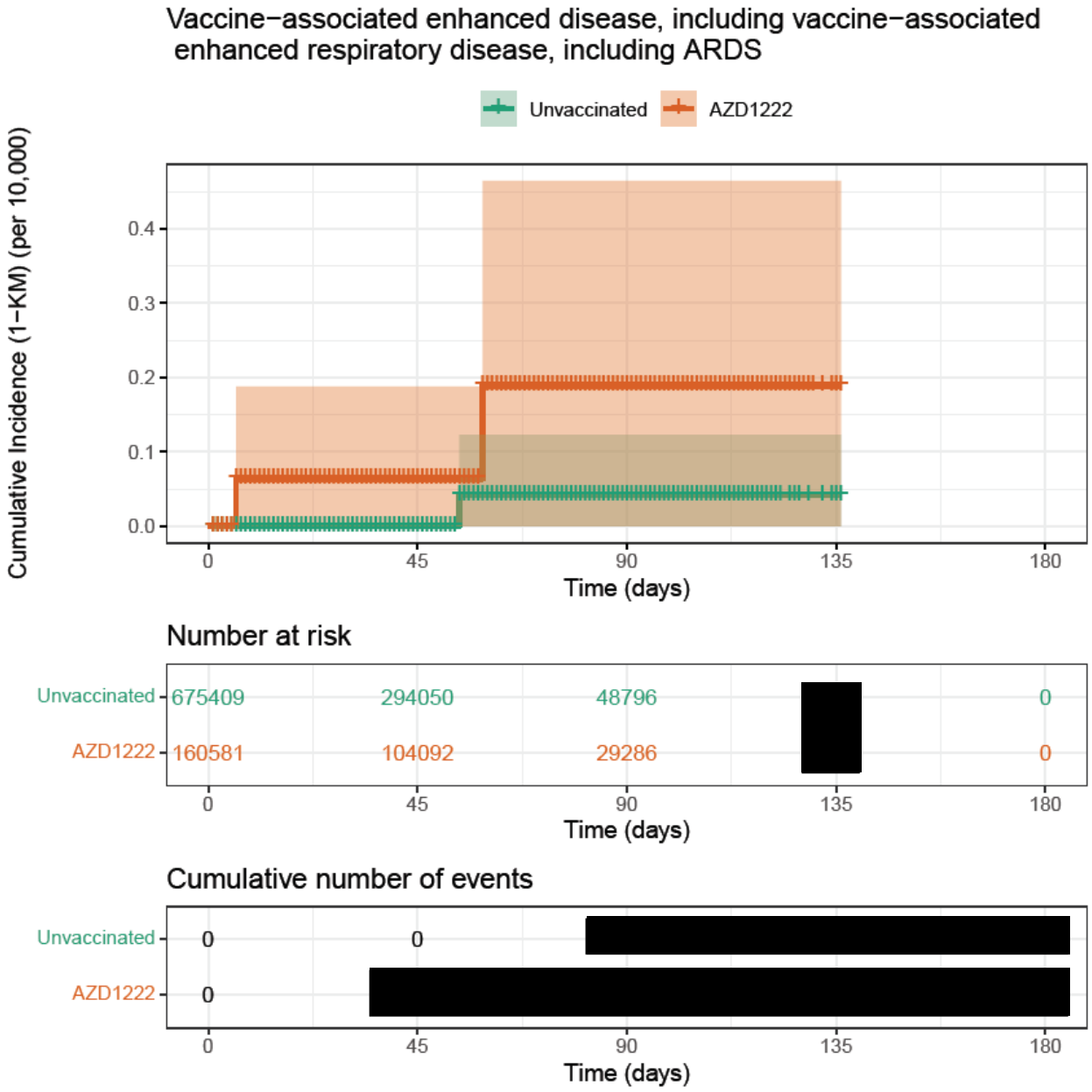


Figure 5.PHARMO. Erythema Multiforme, Cumulative Incidence With Unknown Risk Window

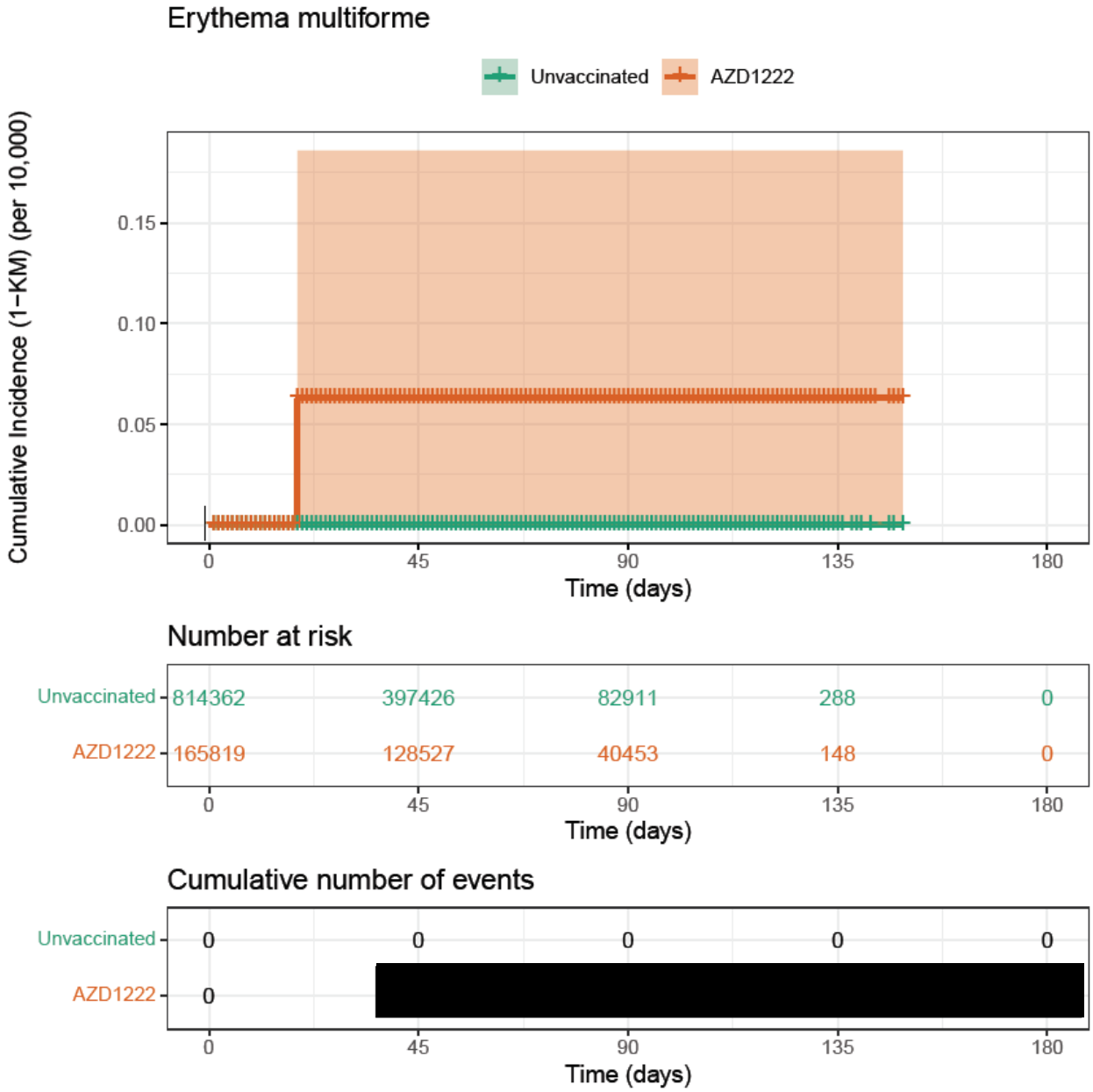
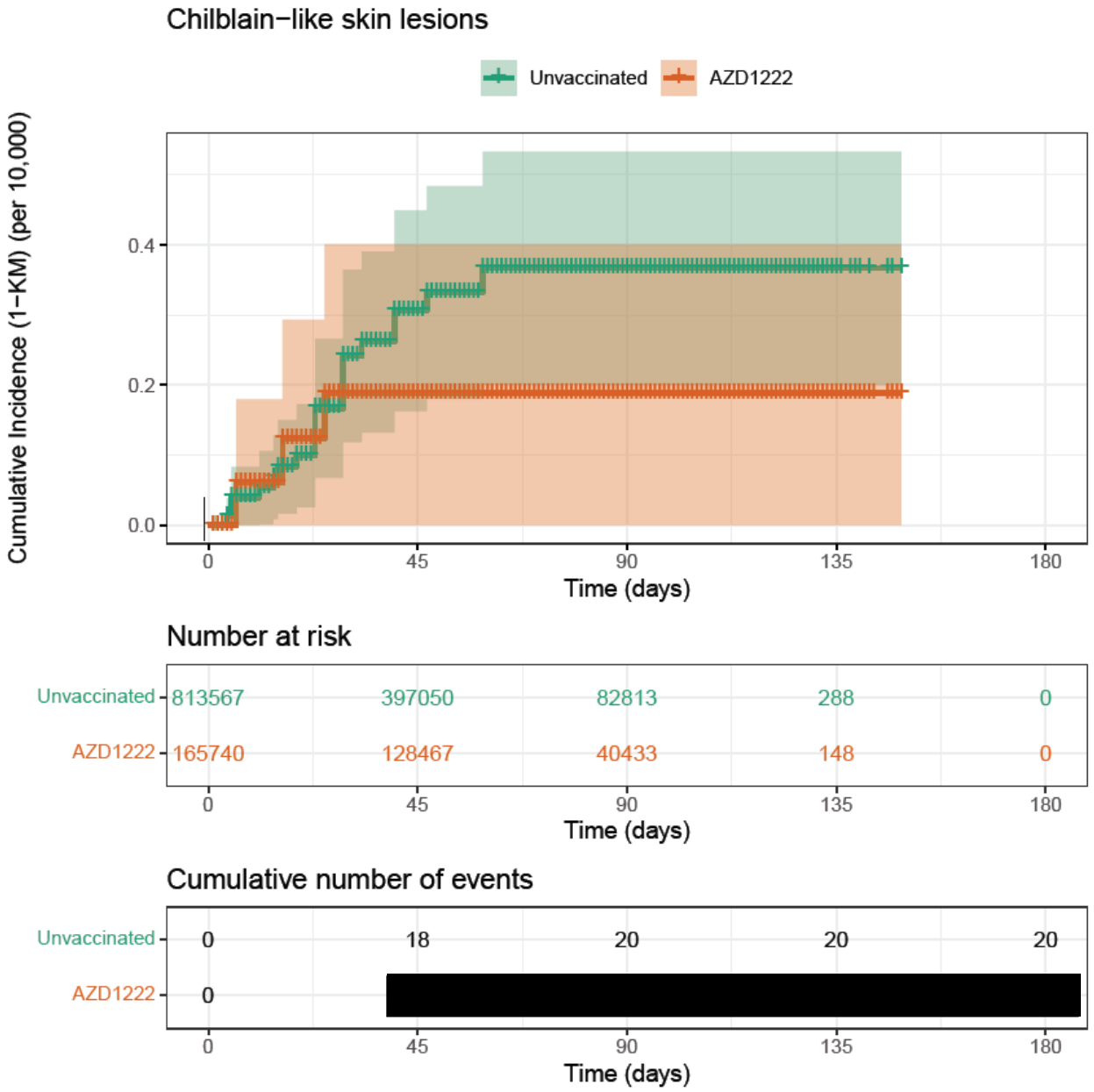


Figure 5.PHARMO. Chilblain-Like Skin Lesions, Cumulative Incidence With Unknown Risk Window



B 3 Standardised Incidence Rates From the ACCESS Project

Incidence rates (95% CIs) per 10,000 person-years for adverse events of special interest (AESIs) from ACCESS, standardised to the age distribution of the study population in each data source.

Adverse event of special interest	Age-standardised IR (95% CI) per 10,000 PY			
	CPRD	SIDIAP	ARS Toscana	PHARMO
Myasthenia gravis	NA	NA	NA	NA
Thrombosis without thrombocytopaenia	22.02 (21.57-22.47)	28.40 (27.01-29.80)	28.71 (26.92-30.50)	7.61 (6.29-8.93)
Thrombosis with thrombocytopaenia syndrome	0.02 (0.01-0.03)	0.02 (0.00-0.05)	0.17 (0.03-0.31)	0.14 (0.00-0.32)
Narcolepsy	0.10 (0.07-0.13)	0.13 (0.04-0.23)	0.03 (0.00-0.09)	0.02 (0.00-0.08)
Thrombocytopaenia with associated bleeding	NA	NA	NA	NA
Autoimmune thyroiditis	NA	NA	NA	NA
Acute aseptic arthritis	0.17 (0.13-0.21)	NA	NA	NA
Guillain-Barré syndrome	0.22 (0.17-0.26)	0.35 (0.19-0.50)	0.61 (0.35-0.88)	0.22 (0.00-0.45)
Thrombocytopaenia	2.59 (2.43-2.74)	11.08 (10.21-11.95)	4.37 (3.67-5.07)	3.06 (2.23-3.90)
Capillary leak syndrome	NA	NA	NA	NA
Postural orthostatic tachycardia syndrome	NA	NA	NA	NA
Acute cardiac injury including microangiopathy, cardiogenic shock, heart failure	19.02 (18.61-19.44)	17.39 (16.30-18.48)	63.48 (60.83-66.14)	16.19 (14.27-18.11)
Stress cardiomyopathy	NA	0.02 (0.00-0.06)	1.36 (0.97-1.75)	NA
Myocardial infarction	NA	NA	NA	NA
Myocarditis/pericarditis	1.56 (1.44-1.68)	2.00 (1.63-2.37)	4.14 (3.46-4.82)	0.65 (0.26-1.03)
Acute pancreatitis	NA	NA	NA	NA
Acute kidney injury	15.80 (15.42-16.18)	53.76 (51.84-55.67)	33.68 (31.74-35.61)	26.42 (23.97-28.87)
Acute liver injury	0.89 (0.80-0.98)	3.78 (3.27-4.29)	3.73 (3.09-4.38)	1.39 (0.83-1.96)

Adverse event of special interest	Age-standardised IR (95% CI) per 10,000 PY			
	CPRD	SIDIAP	ARS Toscana	PHARMO
Multiple sclerosis, and other demyelinating disorders	NA	NA	NA	NA
Transverse myelitis	0.11 (0.07-0.14)	0.05 (0.00-0.10)	0.12 (0.01-0.24)	0.02 (0.00-0.08)
Encephalitis (including ADEM)	0.32 (0.27-0.38)	0.21 (0.09-0.33)	0.93 (0.60-1.25)	0.13 (0.00-0.31)
Other peripheral and polyneuropathies	NA	NA	NA	NA
Generalised convulsions	8.53 (8.25-8.82)	6.28 (5.63-6.94)	14.11 (12.85-15.36)	5.46 (4.34-6.57)
Optic neuritis/neuromyelitis optica spectrum disorder	NA	NA	NA	NA
Bell's palsy	NA	NA	NA	NA
Fibromyalgia	NA	NA	NA	NA
Chronic fatigue syndrome/ME/PVFS	NA	NA	NA	NA
Anosmia, ageusia	3.02 (2.86-3.19)	3.75 (3.24-4.26)	0.01 (0.00-0.04)	0.01 (0.00-0.06)
Type III hypersensitivity reactions	NA	NA	NA	NA
Anaphylaxis	1.69 (1.56-1.81)	0.98 (0.72-1.24)	0.86 (0.55-1.17)	0.37 (0.08-0.66)
Rhabdomyolysis	NA	NA	NA	NA
Multisystem inflammatory syndrome in adults/children	0.00 (0.00-0.01)	0.00 (0.00-0.01)	0.00 (0.00-0.01)	0.01 (0.00-0.04)
Sudden death	0.13 (0.10-0.17)	12.14 (11.23-13.05)	0.22 (0.06-0.38)	NA
Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease, including ARDS	NA	NA	NA	NA
ARDS	3.07 (2.90-3.23)	0.56 (0.36-0.75)	5.95 (5.13-6.76)	4.03 (3.07-4.99)
Erythema multiforme	0.55 (0.47-0.62)	0.50 (0.31-0.68)	0.75 (0.46-1.04)	0.03 (0.00-0.12)
Chilblain-like skin lesions	1.12 (1.02-1.23)	1.13 (0.85-1.40)	0.01 (0.00-0.05)	0.00 (0.00-0.03)

ADEM, acute disseminated encephalomyelitis; ARDS, acute respiratory distress syndrome; ARS Toscana, Regional Health Agency of Tuscany; CI, confidence interval; CPRD, Clinical Practice Research Datalink; IR, incidence rate; ME, myalgic encephalitis; NA, not available; PHARMO, PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research; PVFS, postviral fatigue syndrome; PY, person-years; SIDIAP, Information System for Research in Primary Care.