RWE to support Regulatory Decision-Making

6th EFSPI regulatory statistics workshop

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Disclaimer

The views expressed in this presentation are mine and should not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties

The presenter does not have any conflict of interests.

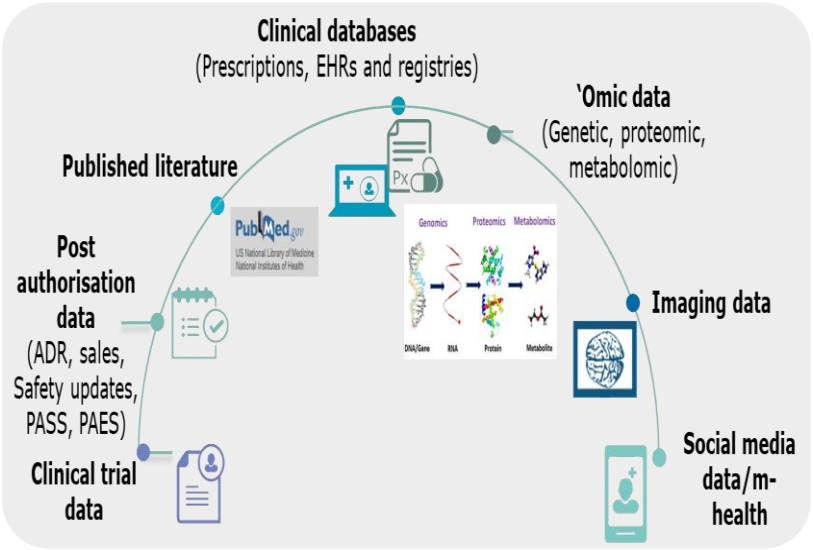
Overview presentation

RWE in a regulatory context

Regulatory use cases of RWE

- Post Authorisation
- Marketing Authorisation Application
- Drug Development
- Health crisis emergencies

Conclusion

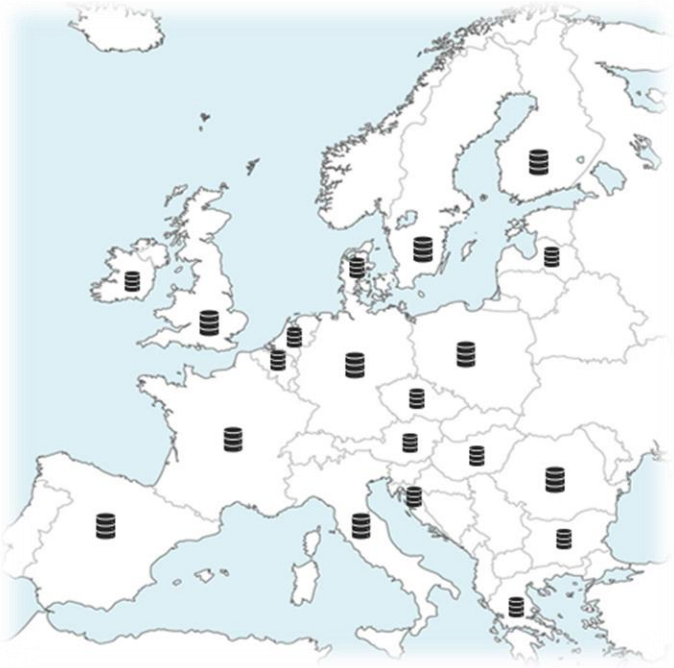


RWE opportunities in a regulatory context

- **Real-World Evidence** (RWE) may support valid regulatory decisions on benefits and risks of authorised medicinal products
- Increased use of RWD: acceptance now beyond post-authorisation safety monitoring → **use cases** along the **medicines regulatory pathway**
- Regulators worldwide have established systems for generating the evidence needed: Sentinel, CNODES, **EMA in-house databases** and **framework contracts**
- In some circumstances, decisions cannot wait, data and analysis need to be quickly available
  - **Public health emergencies (COVID 19)**

EMA Inhouse Databases (RWD)

1) Inhouse databases (GP)
   - IMS Health Germany and France
   - THIN-UK
   - 3 extra databases focus on hospital data
2) EMA funded projects
   - Greater diversity (source, type, location)
3) DARWIN EU 2023
   - Network of data, expertise and services, not database
   - EU spread



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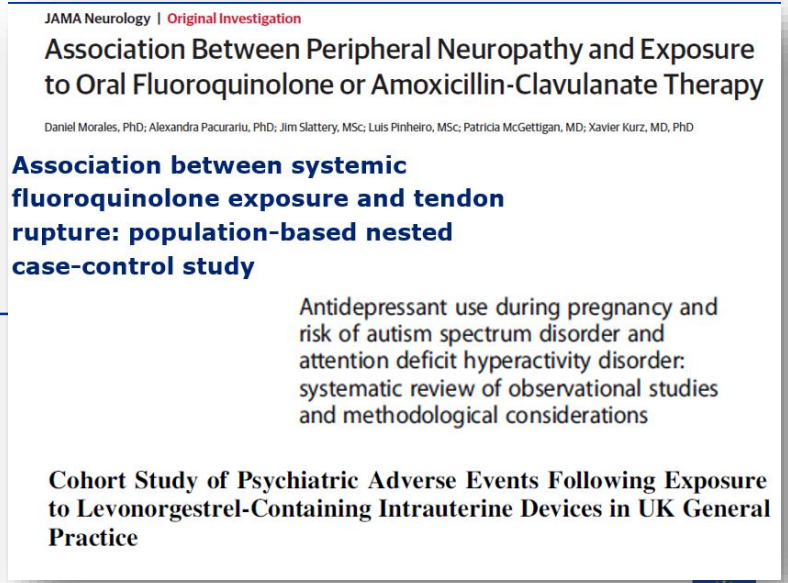
RWE to support safety of medicines – Scientific Committees


JAMA Neurology | Original Investigation

Association Between Peripheral Neuropathy and Exposure to Oral Fluoroquinolone or Amoxicillin-Clavulanate Therapy

Daniel Morales, PhD; Alexandra Pacurariu, PhD; Jim Slattery, MSc; Luis Pinheiro, MSc; Patricia McGettigan, MD; Xavier Kurz, MD, PhD

Association between systemic fluoroquinolone exposure and tendon rupture: population-based nested case-control study

Antidepressant use during pregnancy and risk of autism spectrum disorder and attention deficit hyperactivity disorder: systematic review of observational studies and methodological considerations

Cohort Study of Psychiatric Adverse Events Following Exposure to Levonorgestrel-Containing Intrauterine Devices in UK General Practice

Association between hydrochlorothiazide and incidence skin, lip and oral cancer

- Hydrochlorothiazide (HCTZ) primarily used to manage hypertension, congestive cardiac failure and oedema can cause skin photosensitivity and increase UV light induces DNA damage that could contribute to skin cancer
- Published epidemiological studies from Denmark reported association between HCTZ and an increased risk of skin cancer


Multicenter Study > JAMA Intern Med. 2018 Aug 1;178(8):1120-1122.
doi: 10.1001/jamainternmed.2018.1652.

Association of Hydrochlorothiazide Use and Risk of Malignant Melanoma

unton Pottegård [1], Sidsel Arnspang Pedersen [1 2 3], Sigrun Alba Johannesdottir Schmidt [4], Lisbet Rosenkrantz Hölmich [5], Søren Friis [4 6 7], David Gaist [2 3]


> J Intern Med. 2017 Oct;282(4):322-331. doi: 10.1111/joim.12629. Epub 2017 Jun 6.

Hydrochlorothiazide use is strongly associated with risk of lip cancer

A Pottegård [1], J Hallas [1], M Olesen [1], M T Svendsen [2], L A Habel [3], G D Friedman [3], S Friis [4]

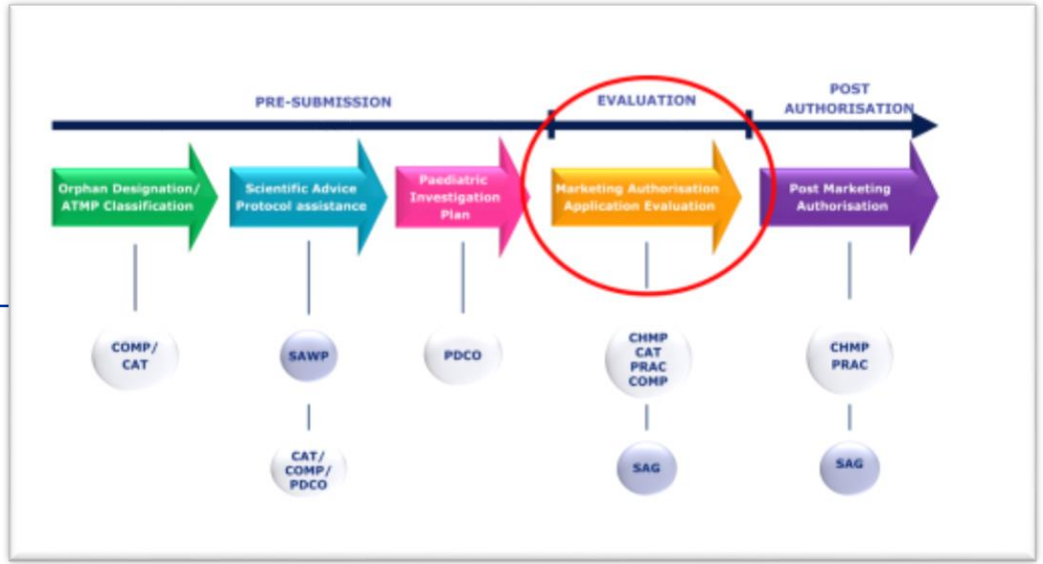
- EMA Pharmacovigilance Risk Assessment Committee (PRAC) discussed a safety review in 2018

Br J Clin Pharmacol. 2020 Jul;86(7):1336-1345. doi: 10.1111/bcp.14245. Epub 2020 Mar 2.

Association between hydrochlorothiazide exposure and different incident skin, lip and oral cavity cancers: A series of population–based nested case–control studies

- To test the potential mechanism that photosensitivity increases the risk of skin cancers by using oral cancer as a negative control
- Rational for the choice
  - Mechanism of action for the risk studied is photosensitivity
  - Cancers arising within the oral cavity will not be exposed to significant UV light while potentially sharing similar risk factors for cancer development
  - Any observed association between HCTZ and oral cancers would raise doubt about the validity of an association between HCZT and skin cancer
- Consistently found no association between HCTZ exposure and oral cancer
- This provides stronger evidence that the observed associations with skin cancer may be causal and related to photosensitivity

RWE to support Marketing Authorisation Applications



CUFENCE https://www.ema.europa.eu/en/medicines/human/EPAR/cufence

* Cufence is a medicine used to treat patients with Wilson's disease in patients intolerant to D-Penicillamine therapy
* Accepted based on Study UNV-TRI-002
    1) Main study; Multicentre **retrospective** study to assess long-term outcomes
        - Single group cohort study based on medical records from large tertiary care centres, 4 EU countries, 90 patients.
        - Strict quality criteria: recruitment stopped at an individual site for reasons of particularly low recruitment, non-compliance to protocol, non-compliance with Good Clinical Practice (GCP), or inadequate data recording

    2) Supportive study; Results of a 12-month **prospective** investigation in 52 patients as continuation of the retrospective study submitted during the course of the procedure, with same objectives.
* Post-authorisation study still required to study the clinical course of hepatic, neurological and psychiatric disease from the time of start up to 24 months of therapy.

Kaftrio: Real World Data Failed To Impress European Reviewers

EU Indication For Vertex's Triple CF Combination Is Narrower Than In US

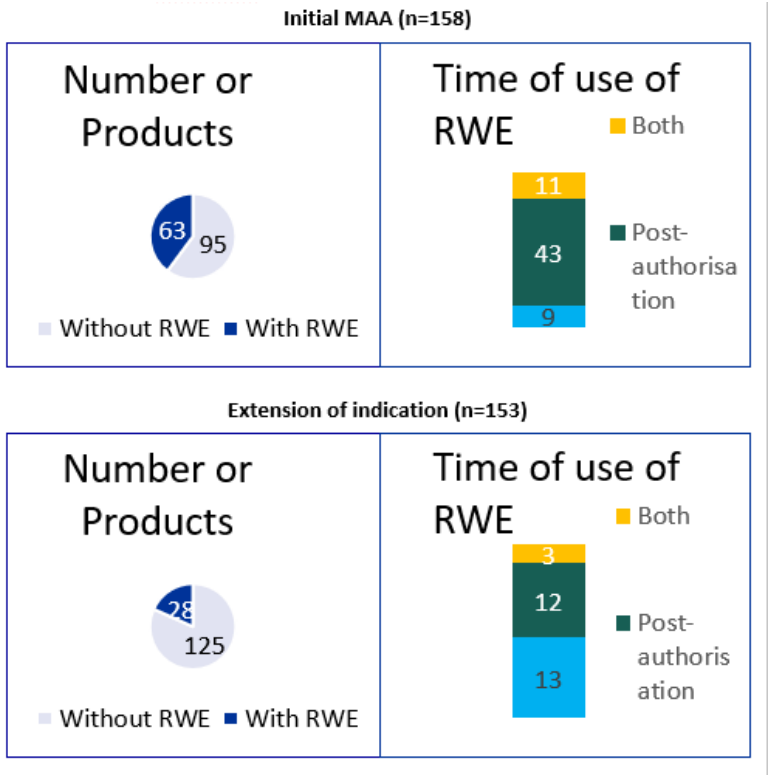
* Kaftrio is a medicine used to treat patients aged 12 years and above who have cystic fibrosis, an inherited disease that has severe effects on the lungs, the digestive system and other organs
* CHMP requested information on different genotypes (F/G, F/RF) through registries to complement the results of the clinical studies for F/MF and F/F

* Additional RWD was provided by the applicant
    -> US Cystic Fibrosis Foundation Patient Registry (F/MF, F/F, F/G and F/RF)

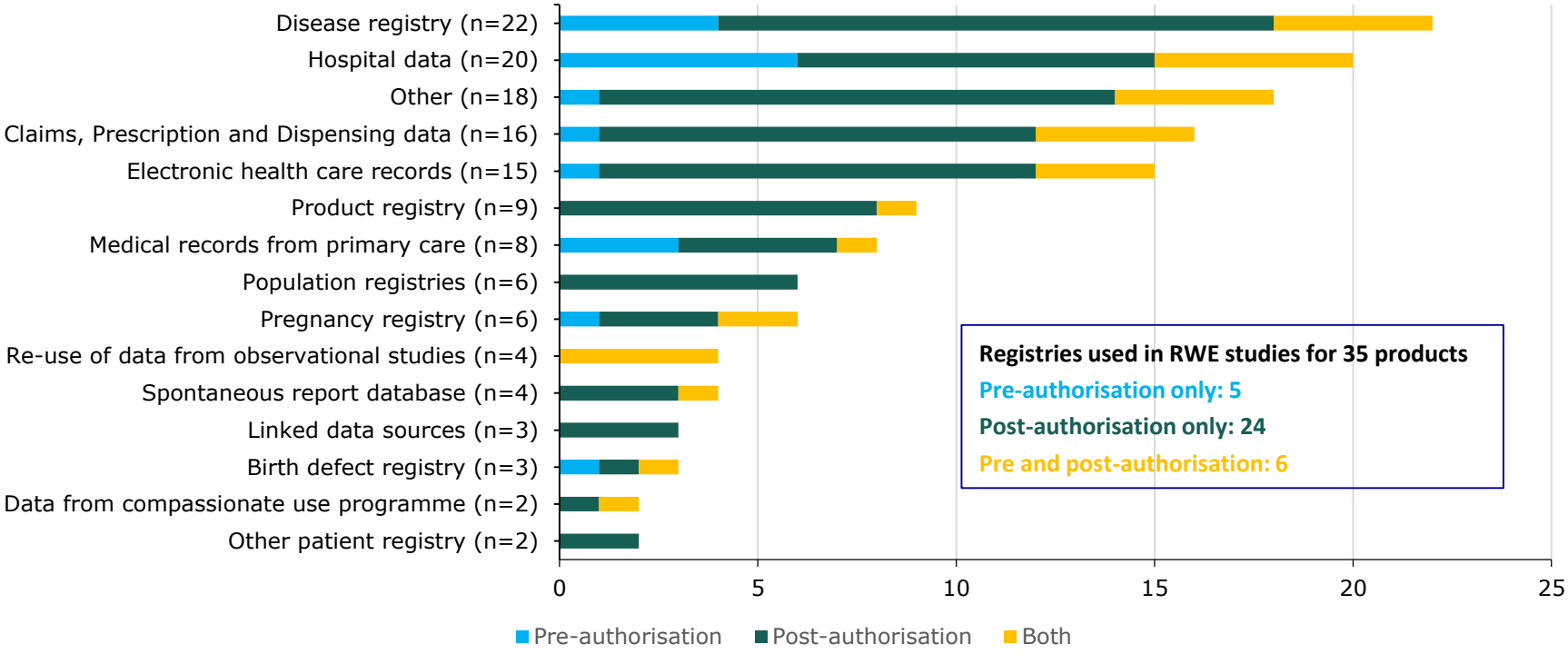
* CHMP rejected registry data and restricted indication to 2 out of 4 phenotypes as not sufficiently detailed with regard to exact modulator therapy, duration of use, as well as specific genotypes and individual patient efficacy data

RWE in MAAs and EoIs

- RWD/RWE used in **40% of MAAs** (mainly post-authorisation) and in **18% of EoIs** (pre- or post-authorisation)
- When used pre-authorisation: mainly supporting study looking at efficacy/effectiveness
- When used post-authorisation: mainly RMP Category 3 (for studies included in RMP) looking at safety



Type or Real Word Datasources used (MAA example)

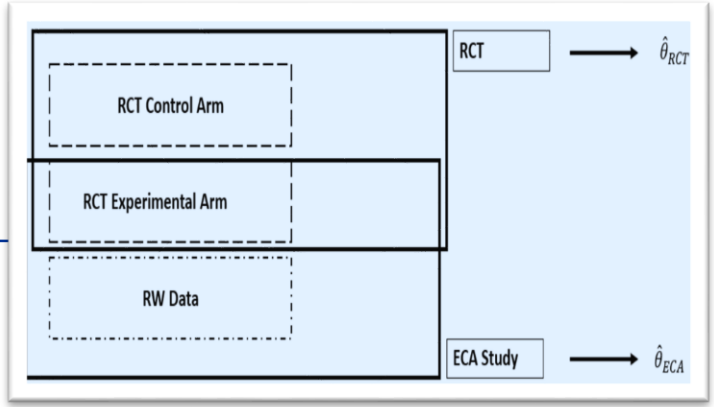


** Example of "Other": follow-up questionnaires of cases of medication errors, medical charts, data sources not specified. "Other" is mainly selected in combination with other specified data sources*

Next steps

- **Initiative 1:**
  - To evaluate the concrete impact and usefulness of RWE in the evaluation and decision-making: how is it used, do we follow consistent approaches?
  - Currently no **framework for using RWE in submissions**: **need for guidance** targeted to various stakeholders (industry, academia, regulators, registry owners etc.)
- **Initiative 2:**
  - To identify a **framework** that helps structuring methodological aspects from observational study designs needed for **causal inference**
    - Increase acceptability of RWE regarding efficacy of medical product
    - Improve reporting of design and analysis of observational studies

RWE to support drug development



Single-arm studies with external comparators (ECA) for cancer drug development (EMA funded study - ongoing)

- **Background**
  - A marked increase regarding the conduct of single-arm trials (SATs) has been observed, especially in the field of *oncology*, also due to the trend towards precision medicine contributing to the rise of new rare diseases.
    - Tenhunen et al. (EU MAA from 2010 to 2019; 22 SATs; 50% orphan indication).
    - Goring et al. (US/EU MAA from 2005 to 2017; 16/43 non RCTs used external control)
- **Objectives**
  - Utilising completed RCTs in the oncology (Prostate/MM) and RWE forming an ECA
  - To assess performance characteristics of different statistical approaches (e.g. PS and non PS weighting approaches)
  - To assess how various settings of data completeness/unmeasured confounding impact the performance measures of statistical approaches
- **Outcomes** (December 2021 Best statistical methods for ECA studies). Future Guidance

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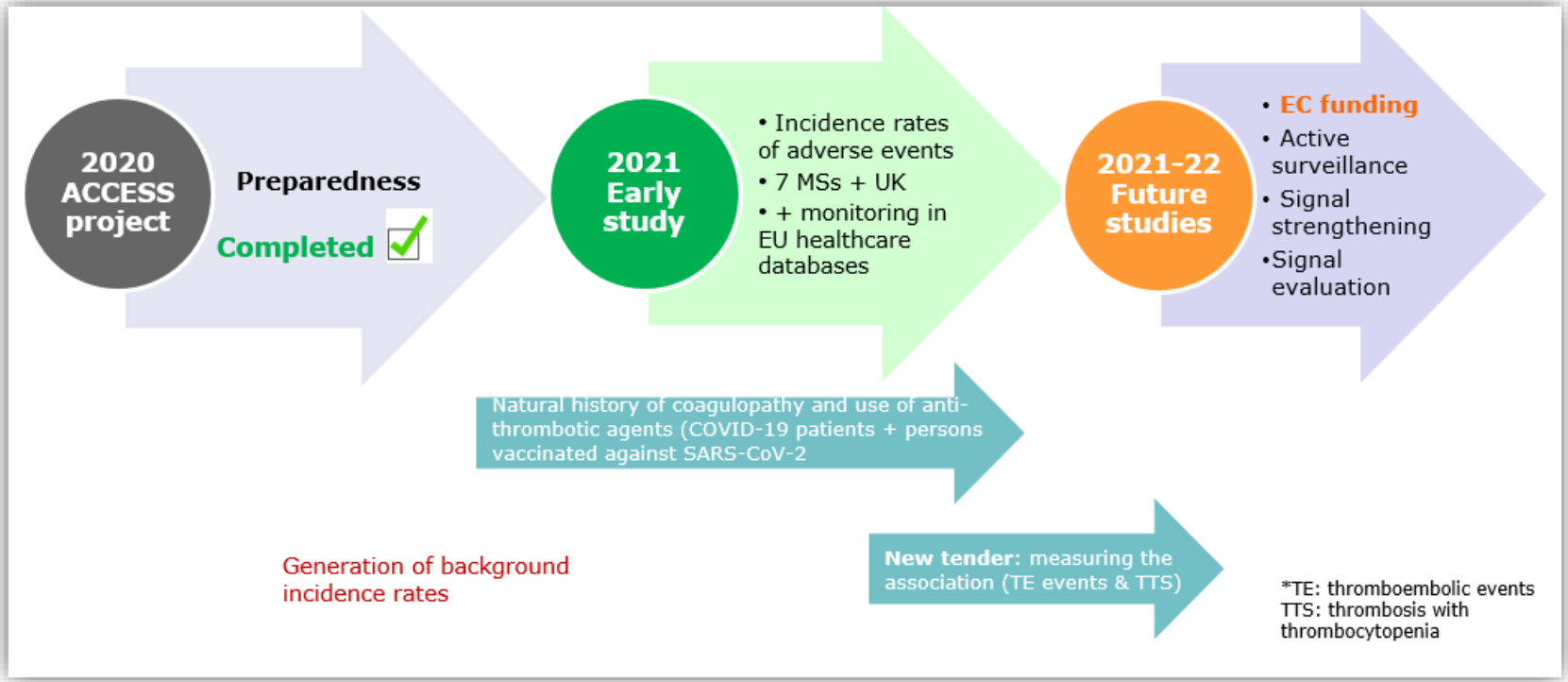
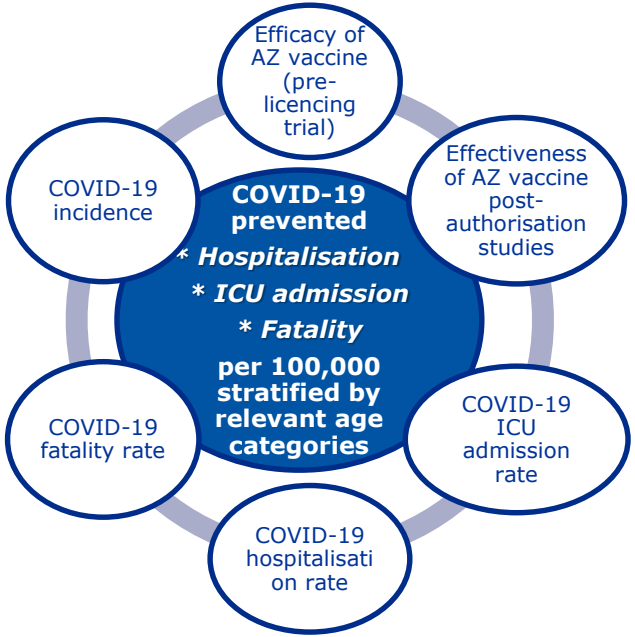
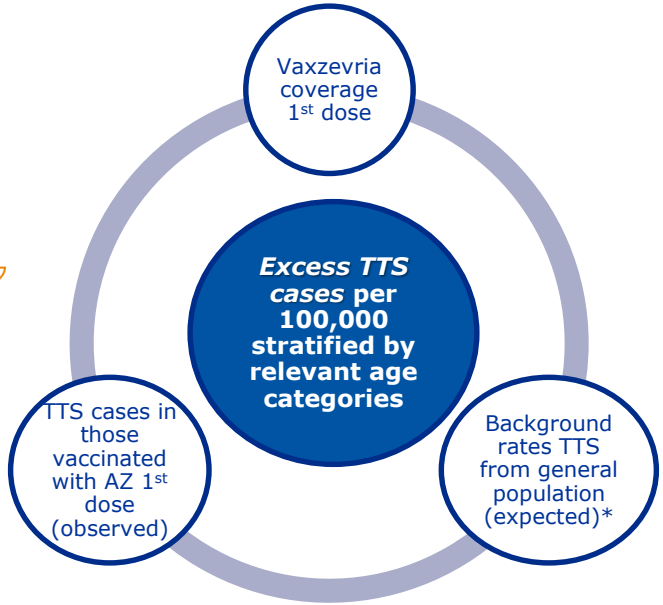
RWE in health crisis planning

COVID-19 vaccines: expanding safety surveillance activities



Benefits of having AZ vaccine versus potential risks associated with AZ vaccine by relevant risk factors: contextualisation exercise (EU/EEA)

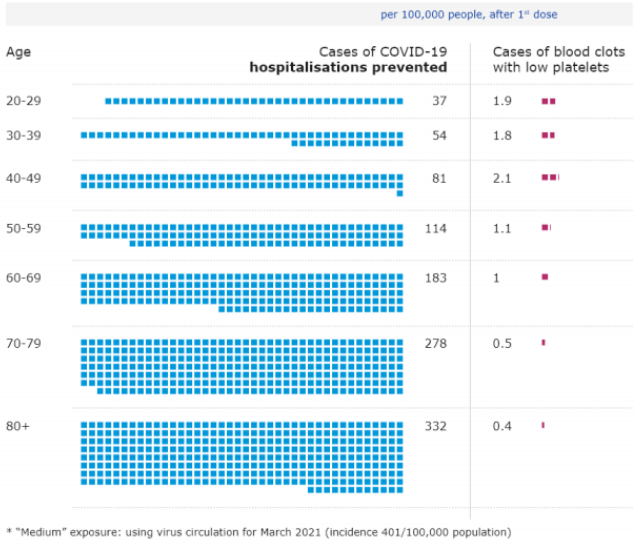




* Background TTS cases close to 0

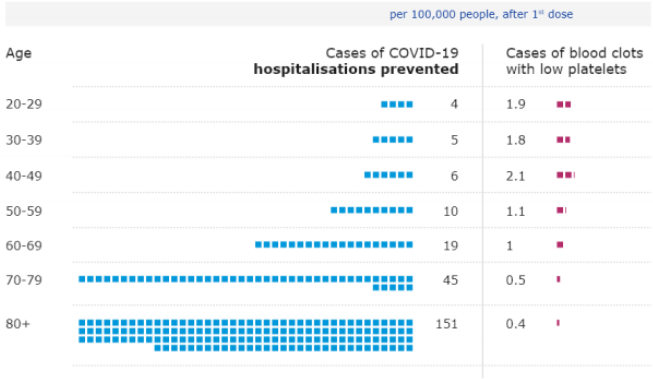
Benefit risk contextualisation

Medium infection rate*



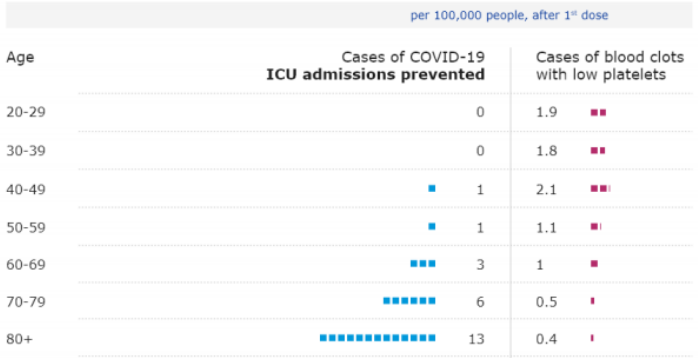
* "Medium" exposure: using virus circulation for March 2021 (incidence 401/100,000 population)

Low infection rate*



* "Low" exposure: using virus circulation for September 2020 (incidence: 55/100,000 population)

Low infection rate*



* "Low" exposure: using virus circulation for September 2020 (incidence: 55/100,000 population)

Benefits depending on age, infection rate and parameter of interest

Conclusion

- Use cases demonstrate the use of RWE along the medicines regulatory pathway
- However, best pharmacoepidemiological and analytical methods are to be used
  - Confounding by indication, selection and information bias, small sample sizes, issues of data quality and data analysis and other limitations of observational evidence seem to be nearly insurmountable obstacles *(http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtm)*
- Need to focus on strengthening all steps from selection of data sources to assessment of evidence to improve validity, reliability, transparency and speed
- Criteria for acceptability of RWE to inform decision making (adequate, accurate, valid, consistent, replicable, timely) *(Cave et al., Clinical Pharmacology & Therapeutics, March 2019)*
- Importance of complying with regulated (GPP, GVP, GEP…) and non-regulated guidelines (RECORD-PE, ISPOR, ISPE…)

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Thank you for your attention

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