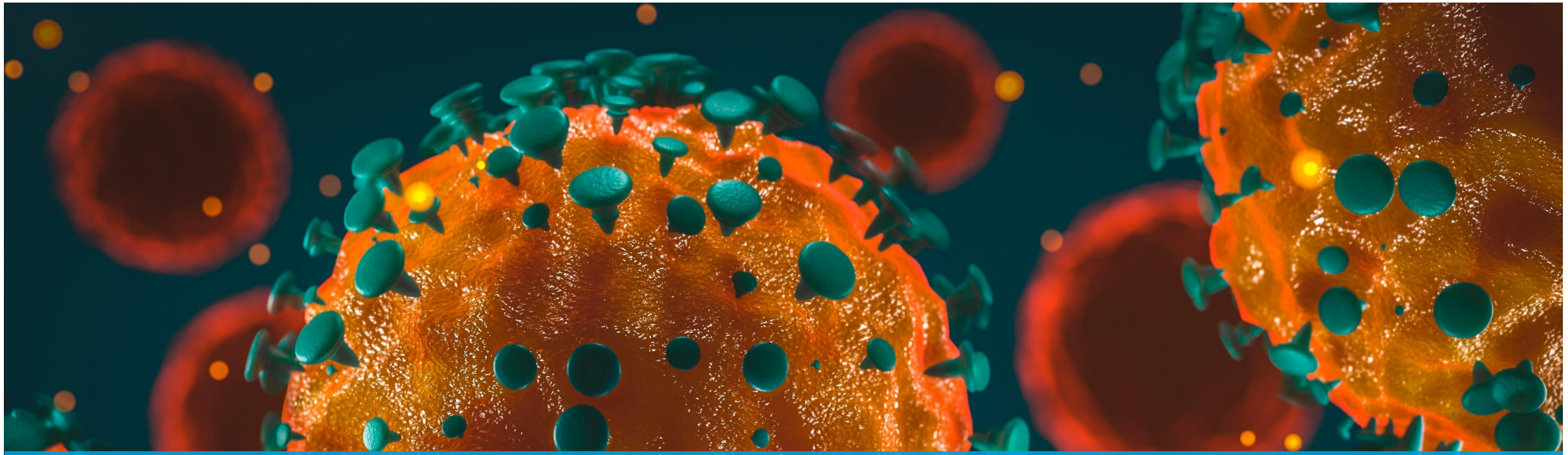

Janssen epidemiology activities to characterize the risk of vaccine-induced TTS

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Pictured: a representation of a coronavirus

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Summary of RWD activities to characterize the risk of vaccine-induced TTS

Executive summary:

- Characterization of the risk of vaccine-induced TTS following administration of the Janssen COVID-19 vaccine is a **priority** that is included in Janssen's post-authorization safety monitoring activities, including through the **use of real-world healthcare databases**
- Unfortunately, availability of information in healthcare databases may be limited (lack information on D-dimer levels, anti-PF4 antibodies, platelet counts, and timing of diagnosis of thrombocytopenia) to establish an algorithm that has sufficient **specificity** for robust assessment of the incidence of vaccine-induced TTS
- Algorithms used (in the literature and by Janssen), in an attempt to address this question, only allow assessing the incidence of the **"co-occurrence of thrombosis and thrombocytopenia"**
- Further analyses show that the baseline demographic characteristics of the "co-occurrence of thrombosis and thrombocytopenia" cases (more older males) is different from those of TTS reported cases (more younger females)
- **Case validation** included in PASS may increase the specificity to identify vaccine-induced TTS in healthcare databases.

Presentation Plan

PART I: TTS reporting rates from Janssen's Global Safety Database

PART II: Operationalization of clinical case definitions in existing real-world healthcare databases

PART III: Rapid Cycle Analysis – Cohort characterization of cases of "co-occurrence of thrombosis and thrombocytopenia" following immunization with the Janssen COVID-19 vaccine in US healthcare databases

PART IV: Data interpretation and conclusion

PART I: TTS reporting rates from Janssen's Global Safety Database (1)

- TTS is a rare and clinically complex disease to diagnose and to identify in real-world databases where key information may be missing to reach the highest case definition level of certainty
- Several TTS clinical case definitions with some differences

PRAC

confirmed, probable, possible,

unlikely or criteria not met

- based on low **platelet count**, **D-dimer levels** and **anti-PF4 antibodies**
- 3 subtypes to categorize thrombosis:
  - arterial,
  - venous,
  - vessel type unspecified and mixed arterial and venous

Brighton Collaboration

Level 1, 2, 3, 4, or 5

CDC

Tier 1 or Tier 2, or Tier 1/2

- based on a low **platelet count** (<150,000 cells per µl)
- with or without anti-PF4 antibodies depending on level of certainty
- differ according to the thrombosis location

PRAC: "Final PRAC assessment report for procedure EMEA/H/C/005737/MEA/014.1, dated 10 June 2021."
Brighton: https://brightoncollaboration.us/thrombosis-with-thrombocytopenia-syndrome-interim-case-definition/
CDC: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/07-COVID-Shimabukuro-508.pdf

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PART I: TTS reporting rates from Janssen's Global Safety Database (2)

Region	Exposure		PRAC/MHRA definition		CDC definition		Brighton definition	
	Doses distributed	Doses administered	Cases[1]	Rate*	Cases[2]	Rate*	Cases[3]	Rate*
World	394,821,400	44,735,821	248 *198*	5.5 *4.4*	105 *89*	2.3 *1.99*	155 *126*	3.5 *2.8*
US	41,506,650	18,746,828	150 *121*	8.00 *6.4*	68 *59*	3.63 *3.1*	105 *87*	5.6 *4.6*
EEA	27,369,500	19,650,744	92 *72*	4.7 *3.7*	35 *28*	1.8 *1.4*	45 *35*	2.3 *1.8*

Rate per million doses of Janssen COVID-19 vaccine administered and in 28-day risk window

Data as of 15 May 2022 (DLP of latest Safety Summary Report)

[1] Cases meeting at least "Possible" criteria

[2] Cases meeting Tier 1/2 criteria

[3] Cases meeting at least Level 3 of diagnostic certainty

Reported TTS

- higher rates in persons <50 years
  - highest in women <50
- 80% of cases occur within 28 days
- No cases reported following homologous booster

PART II: Operationalization of clinical case definitions in existing real-world healthcare databases (1)

- Janssen's post-authorization safety monitoring activities includes assessing the feasibility of using **healthcare real-world databases to assess the risk of vaccine-induced TTS**
- **Algorithms/phenotypes** were developed to identify vaccine-induced TTS cases in real-world healthcare databases (Burn et al., 2022; ACCESS, 2021 (Final Report); Shoaibi et al., 2022) and generate background incidence rates (pre-COVID-19 era: 2017-2019)
- **None of them included an algorithm/phenotype validation process** through medical chart review
- **Key data is missing** (lack information on D-dimer levels, anti-PF4 antibodies and platelet counts) to detect true incident vaccine-induced TTS
- Instead, these algorithms/phenotypes allow detecting the **"co-occurrence of thrombosis and thrombocytopenia"**

EHR: electronic Health Records; EU: Europe; US: United States; DVT: deep vein thrombosis; PE: Pulmonary embolism; MI: Myocardial infarction; CVST: Cerebral sinus venous thrombosis; CAD: coronary artery disease

Burn et al. 2021. Background rates of five thrombosis with thrombocytopenia syndromes of special interest for COVID-19 vaccine safety surveillance: Incidence between 2017 and 2019 and patient profiles from 38.6 million people in six European countries. Pharmacoepidemiol Drug Saf. 2022 May;31(5):495-510. doi: 10.1002/pds.5419. Epub 2022 Feb 27. PMID: 35191114; PMCID: PMC9088543.

ACCESS. 2021. *Background Rates of Adverse Events of Special Interest for Monitoring COVID-1 9 Vaccines (https://zenodo.org/record/5255870#.YrNOw3ZBw2w)*

Shoaibi et al.. Phenotype Algorithms for the Identification and Characterization of Vaccine-Induced Thrombotic Thrombocytopenia in Real World Data: A Multinational Network Cohort Study. Drug Saf. 2022 Jun 2:1–14. doi: 10.1007/s40264-022-01187-y. Epub ahead of print. PMID: 35653017; PMCID: PMC9160850.

PART II: Operationalization of clinical case definitions in existing real-world healthcare databases (2)

References	Burn et al. 2022	ACCESS, 2021 (Final report)	Shoaibi et al., 2022
Study objectives	Background rate	Background rate	Background rate Empirical assessment of phenotype definitions
Study period	2017-2019	2017-2019	2017-2019
Type of data sources	EHR administrative claims: EU	EHR administrative claims: EU	EHR administrative claims: EU, US, Asia Pacific
Algorithm-based definition	Co-occurrence of thrombosis and thrombocytopenia (SNOMED CT codes or a measurement of between 10-15x10^3 platelets/µl) within 10 days prior to the event of interest up to 10 days afterwards. Thrombosis categories: CVST, PE, DVT, Myocardial or Ischemic stroke	Co-occurrence of thrombosis and thrombocytopenia (medical codes from diverse coding systems) within 10 days prior to the event of interest up to 10 days afterwards. Thrombosis categories: VTE (DVT & PE), Arterial (CAD & Ischemic Stroke), VTE or Arterial, CVST	Co-occurrence of embolic or thrombotic arterial or venous event and diagnosis or measurement of thrombocytopenia within 7 days prior to the event of interest up to 7 days afterwards. Thrombosis categories (13 subtypes including DVT, PE, MI,CVST)
Estimated background rates (per 100,000 person/year)	0.1 - 43.4	0.01 - 9.8	1.6 - 150.7

EHR: electronic Health Records; EU: Europe; US: United States; DVT: deep vein thrombosis; PE: Pulmonary embolism; MI: Myocardial infarction; CVST: Cerebral sinus venous thrombosis; CAD: coronary artery disease

Burn et al. 2022. Background rates of five thrombosis with thrombocytopenia syndromes of special interest for COVID-19 vaccine safety surveillance: Incidence between 2017 and 2019 and patient profiles from 38.6 million people in six European countries. Pharmacoepidemiol Drug Saf. 2022 May;31(5):495-510. doi: 10.1002/pds.5419. Epub 2022 Feb 27. PMID: 35191114; PMCID: PMC9088543.

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PART II: Operationalization of clinical case definitions in existing real-world healthcare databases (3)

- Main findings from these 3 initiatives (Burn et al., 2022; ACCESS, 2021 (Final Report); Shoaibi et al., 2022):
  - Estimated background rates of the "co-occurrence of thrombosis and thrombocytopenia" ranged from 0.01 to 150.7 per 100,000 persons-years with considerable differences across databases
  - Shoaibi et al. (2022) reported inconsistent baseline characteristics between "co-occurrence of thrombosis and thrombocytopenia" cases identified in healthcare databases (men of older age with various comorbidities) and reported TTS cases

Indicate a **lack of specificity of the "co-occurrence of thrombosis and thrombocytopenia" algorithms to detect vaccine-induced TTS**

EHR: electronic Health Records; EU: Europe; US: United States; VTE : venous thromboembolism; DVT: deep vein thrombosis; PE: Pulmonary embolism; MI: Myocardial infarction; CVST: Cerebral sinus venous thrombosis; CAD: coronary artery disease

Burn et al. 2022. Background rates of five thrombosis with thrombocytopenia syndromes of special interest for COVID-19 vaccine safety surveillance: Incidence between 2017 and 2019 and patient profiles from 38.6 million people in six European countries. Pharmacoepidemiol Drug Saf. 2022 May;31(5):495-510. doi: 10.1002/pds.5419. Epub 2022 Feb 27. PMID: 35191114; PMCID: PMC9088543.

ACCESS. 2021. *Background Rates of Adverse Events of Special Interest for Monitoring COVID-19 Vaccines* on Zenodo https://doi.org/10.5281/ zenodo.525587 0.

Shoaibi et al. 2022, Phenotype Algorithms for the Identification and Characterization of Vaccine-Induced Thrombotic Thrombocytopenia in Real World Data: A Multinational Network Cohort Study. Drug Saf. Jun 2:1–14. doi: 10.1007/s40264-022-01187-y. Epub ahead of print. PMID: 35653017; PMCID: PMC9160850.

PART II: Operationalization of clinical case definitions in existing real-world healthcare databases (4)

Development of Janssen's algorithm / phenotype for "co-occurrence of thrombosis and thrombocytopenia" used in Rapid Cycle Analysis

- Review of existing medical code lists (OHDSI, ACCESS)
- PRAC recommendations: Thrombosis with thrombocytopenia subclassification (arterial, venous, vessel type unspecified and mixed arterial and venous)

ACCESS
vACCine covid-19 monitoring readinESS

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

- "Co-occurrence (± 7 days) of thrombosis and thrombocytopenia"
- Stratified according to thrombosis types: arterial, venous or vessel type unspecified
- Clean window of 365 days for thrombosis and 90 days for thrombocytopenia

Signal assessment report on embolic and thrombotic events (SMQ) with COVID-19 vaccine Janssen, dated 06 May 2021. Available on: (Covid-19) vaccine (Ad26.COV2-S Recombinant)- COVID-19 Vaccine Janssen - PRAC Rapp AR & recommendation (europa.eu)

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PART III: Rapid Cycle Analysis – Cohort characterization of cases of “co-occurrence of thrombosis and thrombocytopenia” following immunization with the Janssen COVID-19 vaccine in US healthcare databases (1)

- Characterization of “co-occurrence of thrombosis and thrombocytopenia” cases following immunization with the Janssen COVID-19 vaccine in US healthcare databases (28-day risk window)

- Data Sources

Characteristics	HealthVerity	IBM **MarketScan** Commercial Claims and Encounters (**CCAE**)	Optum Clinformatics (**Optum**)
Country	US	US	US
Type of datasources	Administrative claims EHRs	Administrative claims	Administrative claims
Data availability	Through Jan 2022	Through Oct 2021	Through Sep 2021
Janssen exposure	743,385	356,032	183,196

PART III: Rapid Cycle Analysis (RCA) using real-world databases (2)

- **Demographic characteristics of Janssen vaccinees**: no major differences in measured baseline characteristics between the Janssen COVID-19 vaccinees across databases

	Janssen		
	Health Verity	Market Scan	Optum
Total persons	743,385	356,723	183,196
Age in years (mean, SD)	45.6 (15)	44.9 (13)	44.8 (14)
Gender			
% Female	47	46	44
% Male	53	54	56
% with conditions observed as diagnosis in last year:			
Cancer	3.2	2.8	3.0
Type 2 diabetes	10.7	7.6	7.2
Coronary artery disease	3.5	2.0	2.3
Heart failure	1.8	0.6	0.8
COPD	3.2	0.9	1.2
Obesity	16.6	13.9	13.8
Smoker	9.5	3.8	4.8

PART III: Rapid Cycle Analysis (RCA) using real-world databases (3)

- **Demographic characteristics of "co-occurrence of thrombosis and thrombocytopenia" cases** following immunization with the Janssen COVID-19 vaccine (28-day risk window) in US healthcare databases and **real-world incidence**
  - "Co-occurrence of thrombosis and thrombocytopenia" was overall a **rare event**
  - Majority of "co-occurrence of thrombosis and thrombocytopenia" cases were **males and aged above 50 years old**
  - Among 86 identified "co-occurrence of thrombosis and thrombocytopenia" cases, we observed 61% (52) arterial; 43% (37) venous; 11% (9) vessel type unspecified

Demographic characteristics of "co-occurrence of thrombosis and thrombocytopenia" cases following immunization with the Janssen COVID-19 vaccine (28-day risk window) and real-world incidence

	HealthVerity	MarketScan	Optum
Number of persons	60	18	8
Incidence proportion (per 1,000,000 persons)	81.1	50.7	43.9
Mean age (SD)	56 (13)	55 (8)	60 (6)
% Male	75	61	62
% Female	25	39	38

PART IV: Data Interpretation

- "Co-occurrence of thrombosis and thrombocytopenia" cases following immunization with the Janssen COVID-19 vaccine (28-day risk window) in US healthcare databases:
  - was overall a rare event
  - have different demographics (more older males) than reported TTS (more younger females) from reported TTS (spontaneous reporting), i.e.:
    - Janssen's Global Safety Database (GSD)
    - The US VAERS data (FDA, May 2022 - https://www.fda.gov/media/158318/download)
    - Data from literature: vaccine-induced TTS cases that occurred after adenovector based COVID-19 vaccine were disproportionately mainly females and aged < 50 years old (Hafeez 2021, Palaiodimo 2021, Pavord 2021, Waqar 2021)

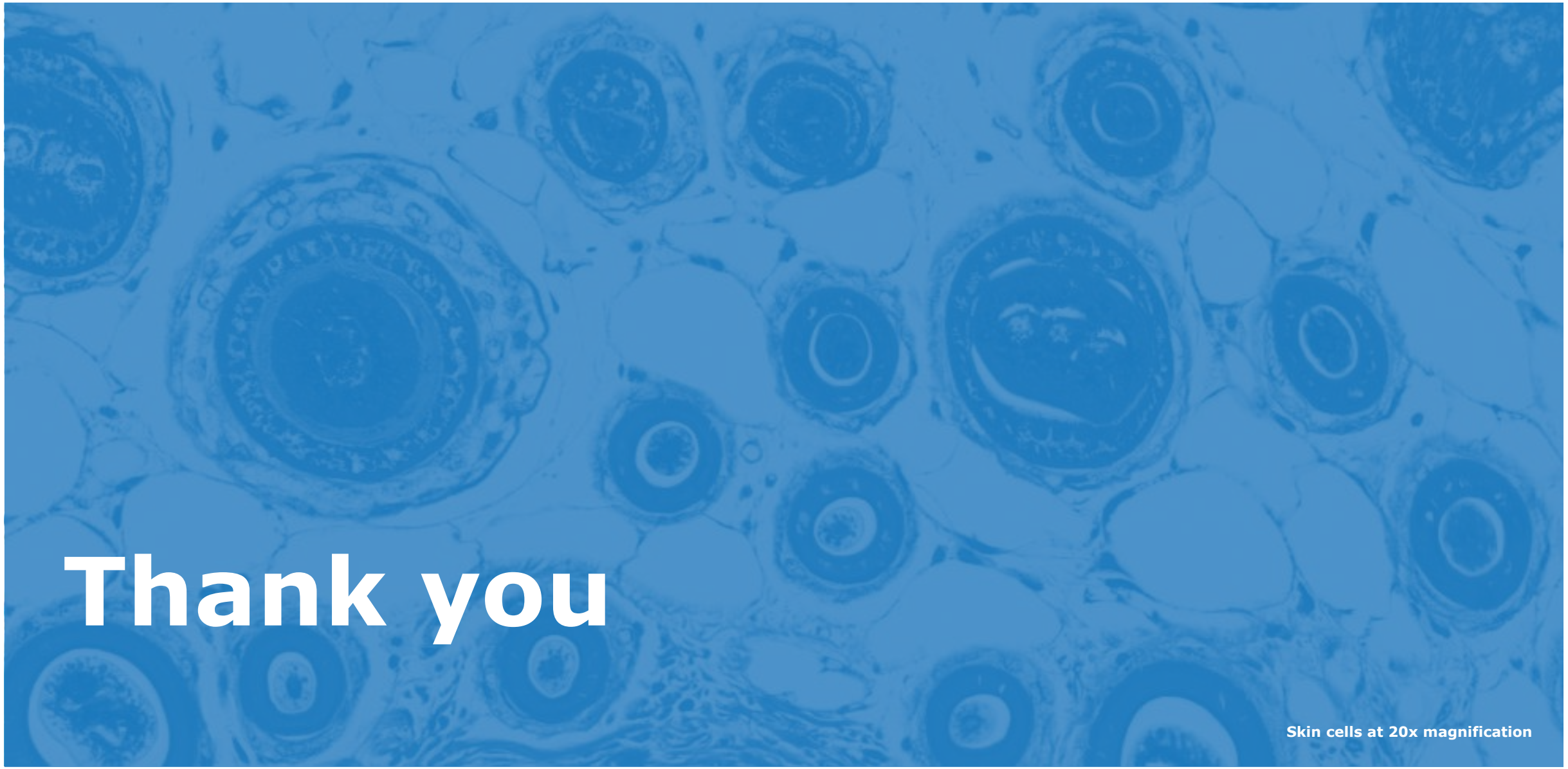
- These findings are in line with conclusions from Shoaibi et al. (2022): inconsistent baseline characteristics between "co-occurrence of thrombosis and thrombocytopenia" cases identified in healthcare databases prior to the COVID-19 era and reported vaccine-induced TTS cases

PART IV: Conclusion

- Lack of specificity of algorithms to identify vaccine-induced TTS: the proportion of '*true vaccine-induced TTS*' cases among the "co-occurrence of thrombosis and thrombocytopenia" cases is unknown.

- Outcome validation: **case ascertainment** process through medical chart review would be needed to characterize risk of vaccine-induced TTS when using existing healthcare databases (insurance claims, EHRs)
  - May increase specificity to identify vaccine-induced TTS
  - Potentially access key lab data such as D-dimer, anti-PF4 assay results, platelet counts (when linked)
  - Potentially allow classification according to existing clinical case definitions
  - This process of case ascertainment will be implemented in the formal ongoing PASS (COV4001 US PASS, COV4003 EU PASS)

Thank you



Skin cells at 20x magnification

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