TTS – insights from pharmacovigilance and epidemiology

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Agenda

Insights from AstraZeneca safety database analyses

- Variability in TTS reporting rate by dose
- Variability in TTS reporting rate by geographic region
- TTS clinical observations

Insights from AstraZeneca epidemiological studies

- TTS background rates from EHR data
- Interim data from a multi-country observational post-authorisation safety study

EHR, electronic health records; TTS, thrombosis with thrombocytopenia syndrome.

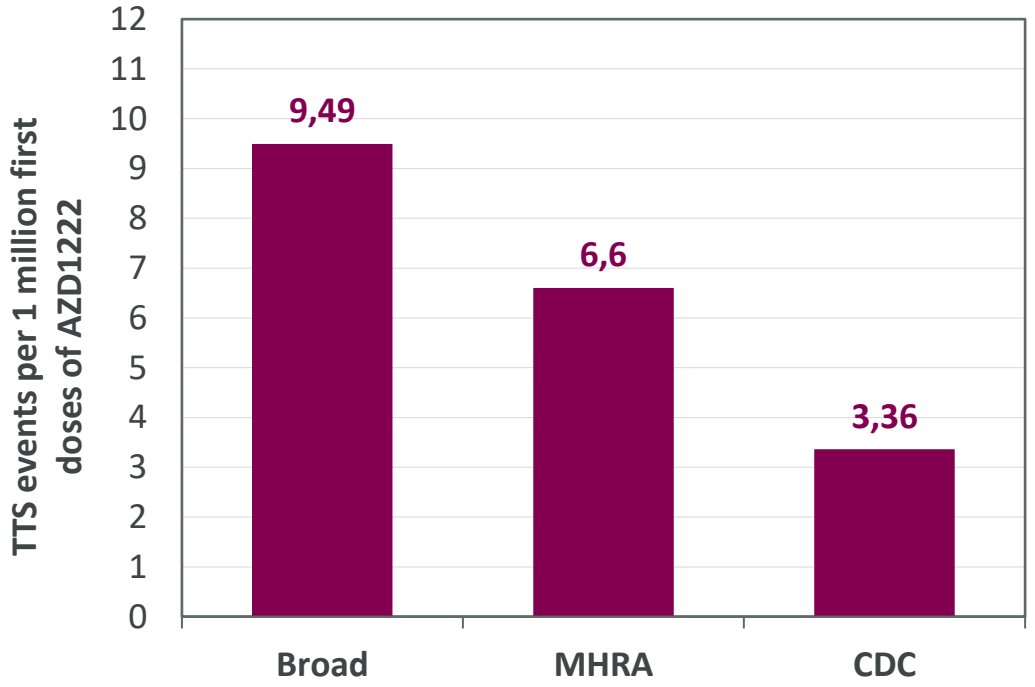
Insights from AstraZeneca safety database analyses

Absence of **consensus on TTS definition** affects data analysis and interpretation

Definitions of TTS used for analysis of reporting rates following COVID-19 vaccine AZD1222 (ChAdOx1 nCoV-19)

- **AstraZeneca safety database:** cumulative data from EU, UK, and Brazil; data cut-off: 28 March 2022
  - **Time window:** 21 days post-vaccination, first dose
- **Broad definition: AE database search[1]** for co-reporting of thromboembolism PTs with thrombocytopenia PTs in ICSRs
- **MHRA definition: clinical / labs / special labs data**
  Cases defined as 'Confirmed', 'Probable', or 'Possible'
- **CDC definition:[2] clinical / location / labs / special labs data**
  Cases defined as Tier 1 or 2

TTS reporting rate using broad, MHRA, or CDC event definitions



1. Soboleva K, et al. Lancet Glob Health. 2022;10(1):e33–e34. 2. NCIRD, Advisory Committee on Immunization Practices. December 2021. https://stacks.cdc.gov/view/cdc/112665

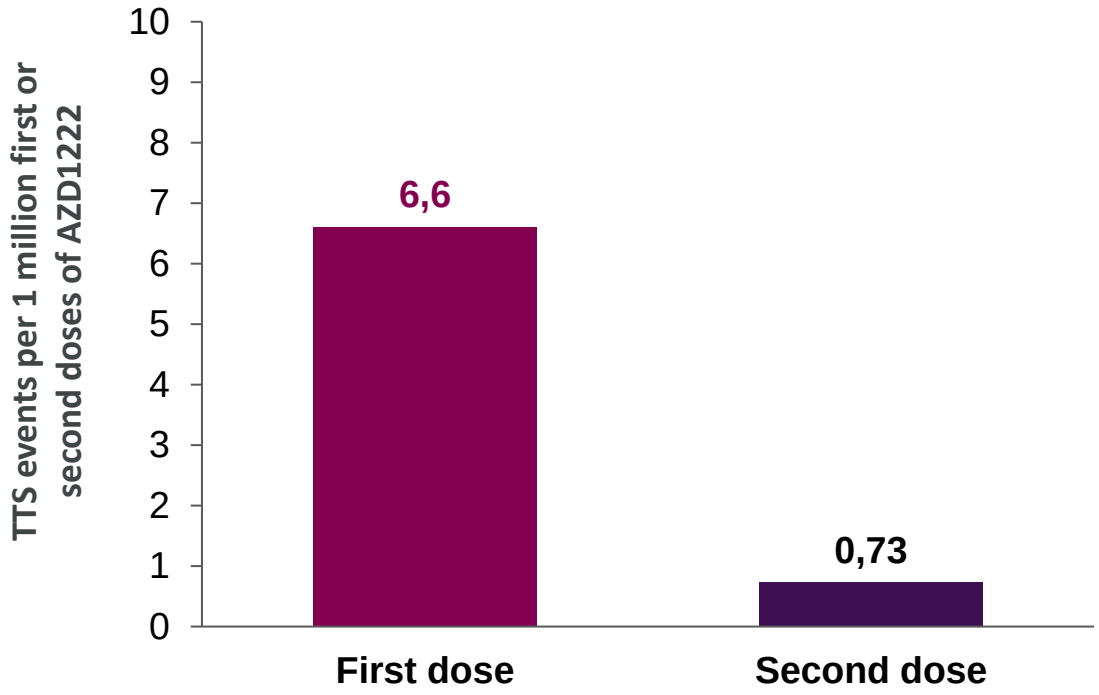
AE, adverse event; CDC – US Centers for Disease Control and Prevention; EU, European Union; ICSR, Individual Case Safety Report; MHRA, Medicines and Healthcare products Regulatory Agency; NCIRD, National Center for Immunization & Respiratory Diseases; PT, Preferred Term; TTS, thrombosis with thrombocytopenia syndrome; UK, United Kingdom.

TTS reporting rates by dose: **rates after the second dose are substantially lower** than after the first dose

AZD1222 TTS reporting rates analysis by dose

- **AstraZeneca safety database:**
  - **Cumulative data from EU, UK, and Brazil**; data cut-off: 28 March 2022
  - **MHRA criteria:** 'Confirmed', 'Probable', or 'Possible
  - **Time window:** 21 days post-vaccination, first dose
- **Data corroborate previously published pattern[1]**

TTS reporting rates post first and second AZD1222 dose



1. Bhuyan P, et al. Lancet. 2021;398(10300):577–578.

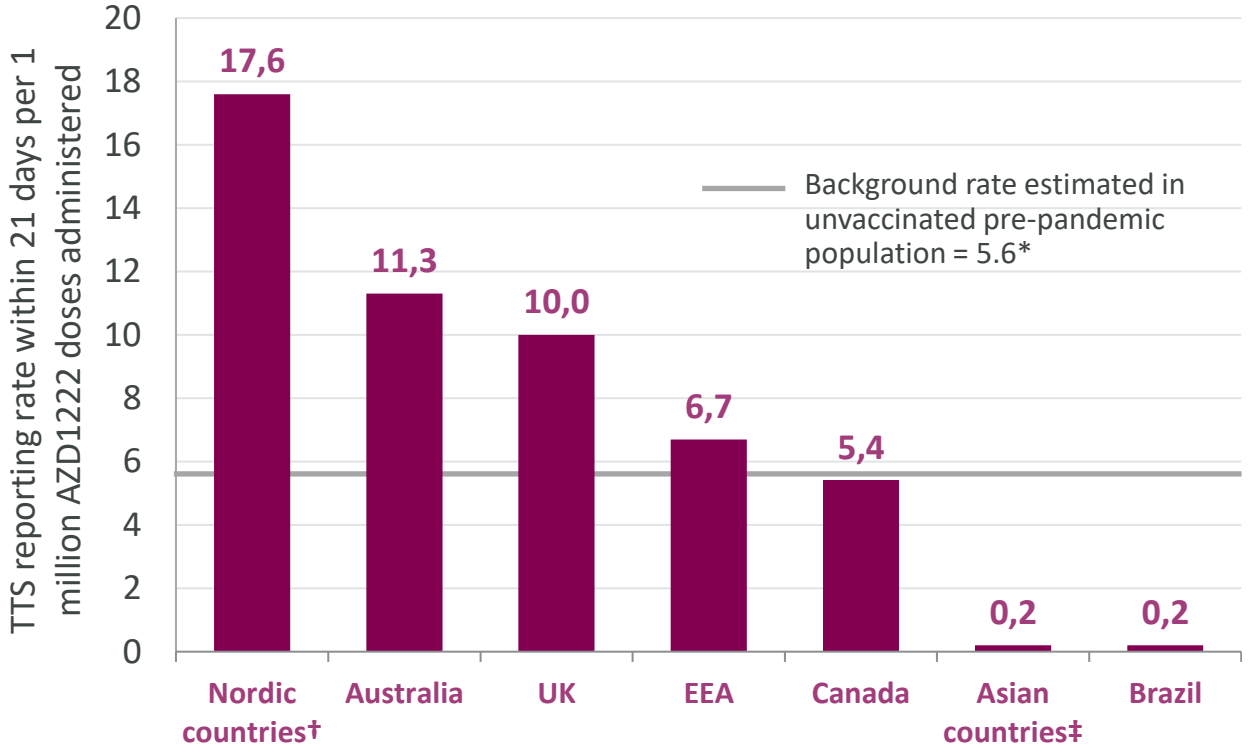
EU, European Union; MHRA, Medicines and Healthcare products Regulatory Agency; TTS, thrombosis with thrombocytopenia syndrome; UK, United Kingdom.

TTS reporting rates by region: **differences in reporting rates observed across geographic regions**

AZD1222 TTS reporting rates analysis by geographic region

- **AstraZeneca safety database:**
  - **Cumulative data for indicated countries**; data cut-off: 31 August 2021
  - **Broad TTS definition:** co-reported thromboembolic events and thrombocytopenia events
  - **Time window:** 21 days post-vaccination
- **Background rate in unvaccinated pre-pandemic population:**
  - Estimated using US Truven MarketScan data, 2019

Reporting rates highest in Nordic countries, UK, and Australia



Soboleva K, et al. Lancet Glob Health. 2022;10(1):e33–e34.

*Thrombocytopenia occurring ±7 days of thrombotic/thromboembolic event. †Denmark, Finland, Iceland, Norway, and Sweden. ‡The Philippines, South Korea, and Taiwan.

EEA, European Economic Area; TTS, thrombosis with thrombocytopenia syndrome; UK, United Kingdom; US, United States.

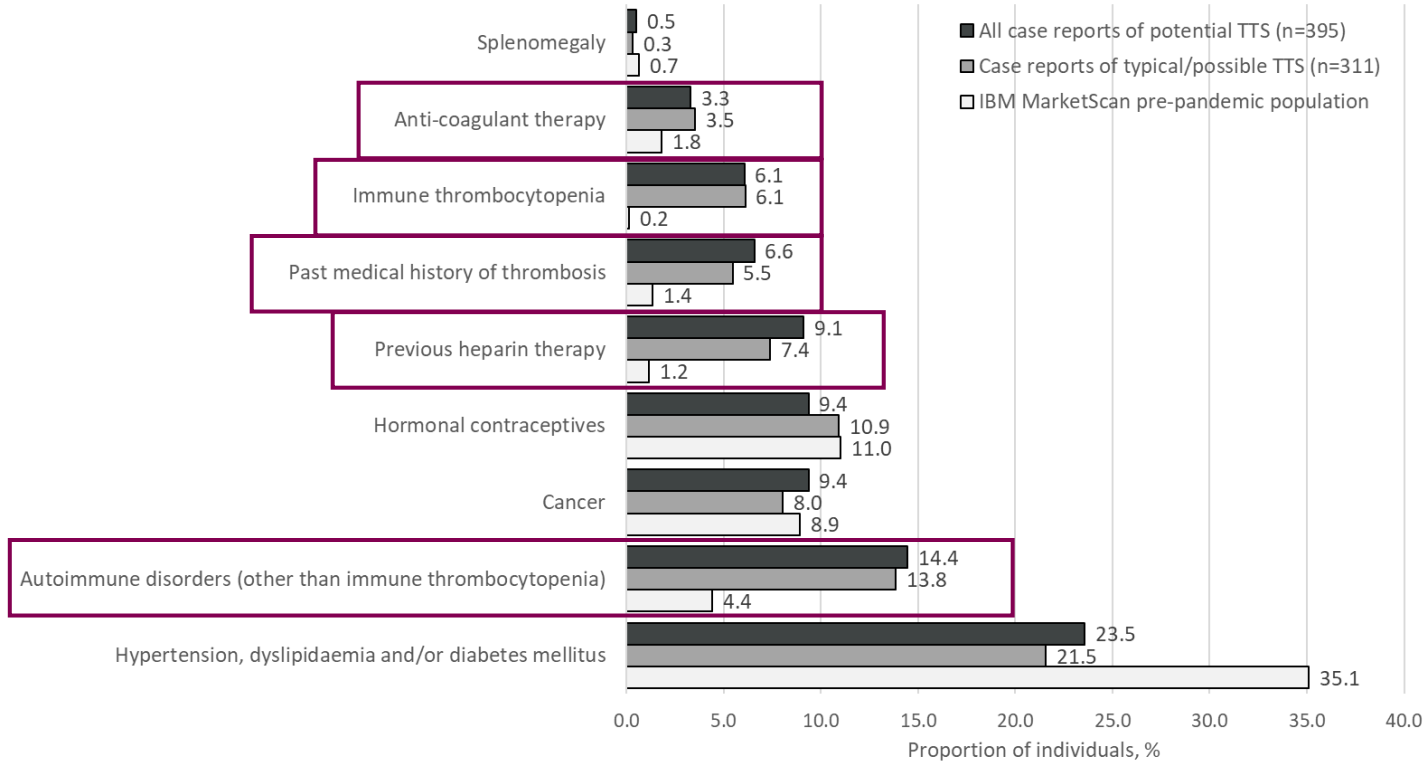
Clinical aspects of TTS

Expert review of TTS cases in AstraZeneca global safety database[1]*

In cases classed as 'typical' / 'possible' TTS by expert adjudication:

- **Most common presenting symptom** was **headache**, reported in 41.2% of cases
  - Reported in 60.7% of cases with CVST
- **61.9%** of cases were in women
- Median age was **50.0 years**
- **Site of thrombosis:** CVST, 44.1%; splanchnic venous thrombosis, 14.6%; thromboses at multiple sites, 26.8%
- **Case fatality rate:** decreased from 39.0% in Feb/Mar to 17.5% in Nov/Dec 2021

Medically relevant comorbidities and medications in TTS cases following AZD1222



1. Laffan MA, et al. Manuscript submitted, post-peer review. 2022.
*Case reports from 1 Feb–26 Apr, 20 May–20 Jun, and 1 Oct–28 Dec 2021.
CVST, cerebral venous sinus thrombosis; TTS, thrombosis with thrombocytopenia syndrome.

Insights from AstraZeneca epidemiological studies

VAC4EU (Vaccine Monitoring Collaboration for Europe)[1] Post-Authorisation Safety Study (PASS)

- Retrospective cohort study based on data from 4 countries (UK, Spain, Italy, the Netherlands) on AESIs
- First interim report included:
  - >5 million people vaccinated with the first dose AZD1222 during Q1/Q2 2021
  - Unvaccinated controls (ratio 1:5), matched by age, sex, geographical region, and prior diagnosis of COVID-19 status
  - TTS defined based on ACCESS;[2] risk window: 42 days post-vaccination

Characteristics of individuals vaccinated with AZD1222

	CPRD Aurum (UK)	SIDIAP (Catalonia, Spain)	ARS Toscana (Italy)	PHARMO (Netherlands)
Number of individuals, millions	4	0.56	0.34	0.16
Median age (IQR)	54 (45, 65)	62 (59, 65)	69 (56, 74)	62 (60, 64)
Female, %	51	55	55	52

1. https://vac4eu.org/covid-19-vaccine-monitoring/
2. https://vac4eu.org/covid-19-tool/

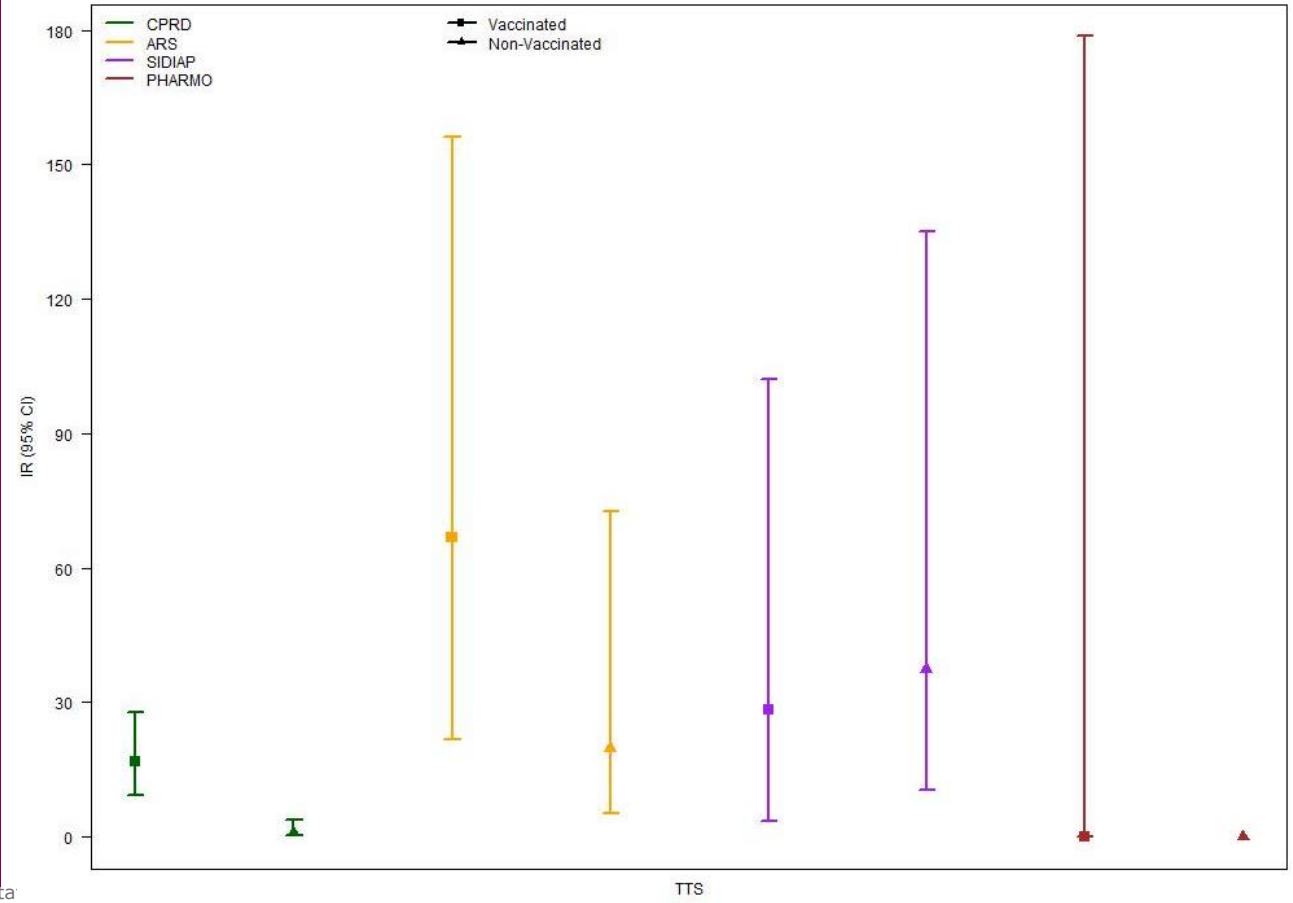
ACCESS, vACCine covid-19 monitoring readinESS; AESI, adverse event of special interest; ARS, Agenzia Regionale di Sanità; CPRD, Clinical Practice Research Datalink; IQR, interquartile range; SIDIAP, Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (Information System for Research in Primary Care); UK, United Kingdom.

Interim data from VAC4EU PASS

TTS cases from 4 European databases: CPRD (UK), SIDIAP (Catalonia, Spain), ARS (Italy), PHARMO (Netherlands)

- The combination of thrombocytopenia with thrombosis was very infrequent in all data sources
  - There were between 0 and 16 events per database
- The validation of TTS events in medical records will be performed in future analyses

Risk (95% CI) per 1 million among vaccinated and matched non-vaccinated individuals (1:5 ratio)
Risk window: 42 days post-vaccination



CI, confidence interval; TTS, thrombosis with thrombocytopenia syndrome.

Concluding remarks

- There is no commonly agreed definition of TTS
- In both the AstraZeneca global safety database and in the EHR PASS, TTS is an extremely rare event following AZD1222 vaccination, thus supporting the overall benefits of vaccination against COVID-19 outweigh the risks
- Reporting rates are lower after the second dose compared to after the first dose of AZD1222, and vary across geographical areas
- Consensus on the definition of TTS is needed to enable consistent analysis and interpretation of existing and emerging data

EHR, electronic health records; PASS, Post-Authorisation Safety Study; TTS, thrombosis with thrombocytopenia syndrome.

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VAC4EU AZD1222 PASS team

Collaborating institutions:

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- DSRU UK
- FISABIO, Spain
- IDIAP, Spain
- PHARMO, Netherlands
- UMCU, Netherlands

Back-up information

MHRA Definition of TTS

Case definition	Thrombosis status	Platelets	D-dimer	Anti-PF4 antibodies
Confirmed	Any venous/arterial thrombosis +	Platelet count < 150 x 10^9/L +	D-dimer > 4000 ng/mL +	Anti-PF4 antibodies
Probable	Any venous/arterial thrombosis +	Platelet count < 150 x 10^9/L +	D-dimer > 4000 ng/mL	
Possible	Any venous/arterial thrombosis +	Platelet count < 150 x 10^9/L OR wording compatible with platelet count decreased		
Unlikely	Criteria met for any of the above BUT alternative diagnosis more likely to explain the event			
Criteria Not Met	One or none of the criteria are met			

MHRA, Medicines and Healthcare products Regulatory Agency; PF4, platelet factor 4; TTS, thrombosis with thrombocytopenia syndrome.

CDC working case definition for TTS following COVID-19 Vaccine

TTS category	Thrombosis location	Platelet count	Positive PF4 ELISA* test required?
Tier 1	Unusual location, e.g., CVST, abdominal venous or arterial thrombosis	<150,000 cells/µL	No
Tier 2	Only in 'typical' location(s), e.g., pulmonary embolism, deep vein thrombosis of extremity	<150,000 cells/µL	Yes

- Reports where only thrombosis is ischemic stroke or myocardial infarction are excluded
- Cases with concurrent COVID-19 infection excluded

*PF4 ELISA: platelet factor 4 enzyme-linked immunosorbent assay

NCIRD, Advisory Committee on Immunization Practices. December 2021. https://stacks.cdc.gov/view/cdc/112665