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RISK BENEFIT IN CONTEXT FOR TTS EVENTS APPLIED TO THE JOHNSON & JOHNSON VACCINE

SUMMARY FOR THE INTER-MINISTERIAL CONFERENCE ON PUBLIC HEALTH

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This document is a rapid adaptation of the EMA risk benefit contextualisation for thrombocytopenia syndrome (TTS) after vaccination for Vaxzevria™ to the Johnson & Johnson vaccine.

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1 OVERVIEW

Problem

How does the incidence rate of thrombosis with thrombocytopenia syndrome (TTS) after vaccination with the Johnson & Johnson vaccine compares to the benefit of avoiding hospitalisation, ICU admission or death by vaccinating with the Johnson & Johnson vaccine?

Plan

EMA published a risk benefit contextualisation of the Vaxzevria™ vaccine, focusing on the risk of TTS on the 23rd of April 2021. The analysis aimed at informing national decisions on the roll out of the vaccine, taking into account the pandemic situation.

The current analysis adapts the contextualisation of benefits and harms to the Johnson & Johnson vaccine:

- Potential harms were assessed based on the number of cases of thrombosis with thrombocytopenia syndrome (TTS) in patients having received J&J vaccine.
- Potential benefits are defined as:
  - Prevention of hospitalisation.
  - Prevention of ICU admission.
  - Prevention of death.

We reuse the EU estimates on hospitalisation, ICU and death, provided by EMA for conducting the benefit risk contextualisation exercise.

We will explicitly point out and argument when we adapt the analysis. Otherwise, definitions and choices are the same as reported on https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-benefits-risks-context.

Data

Thrombosis with thrombocytopenia syndrome (TTS)

USA Centres for Disease Control and Prevention (CDC) reported events on May 24 (unpublished preliminary results).

Hospitalisations

Hospitalisation incidence as provided by EMA to EU member states in the risk benefit contextualisation of Vaxzevria™ vaccine for TTS.

ICU

ICU admission incidence as provided by EMA to EU member states in the risk benefit contextualisation of Vaxzevria™ vaccine for TTS.

Death

Incidence of death as provided by EMA to EU member states in the risk benefit contextualisation of Vaxzevria™ vaccine for TTS.

Analysis

The analysis is performed for three different epidemiological scenarios, similar to the EMA risk benefit contextualisation of TTS after Vaxzevria™ vaccine:

Low infection rate

Using virus circulation in the EU of September 2020: 55 per 100 000 people.

Medium infection rate

Using virus circulation in the EU of March 2021: 401 per 100 000 people.

High infection rate

Using virus circulation in the EU of January 2021: 886 per 100 000 people.

The analysis uses the following variates:

Risk on thrombosis with thrombocytopenia syndrome (TTS)

Calculation of the number of TTS events per 100 000 people vaccinated with the Johnson & Johnson vaccine.

Benefit of preventing hospitalisations

Calculation of the estimated number of prevented hospitalisations per 100 000 people if vaccinated with the Johnson & Johnson vaccine.

Benefit of preventing ICU admissions

Calculation of the estimated number of prevented ICU admissions per 100 000 people if vaccinated with the Johnson & Johnson vaccine.

Benefit of preventing death

Calculation of the estimated number of prevented deaths per 100 000 people if vaccinated with the Johnson & Johnson vaccine.

Based on the Johnson & Johnson vaccine phase 3 trial results, an 85% reduction of hospitalisation, ICU admission and mortality was modelled (see methods section for details).

The analysis takes into account possible underreporting of TTS (see methods section for details).

Because of different assumptions on vaccine efficacy and underreporting, the results cannot be directly comparted to those of EMA risk benefit contextualisation of TTS after Vaxzevria™ vaccine.

Next sections

2. Risk benefit comparison per infection rate scenario for each of the three possible benefits.
3. Method section that provides an overview of the choices made.

2 RISK BENEFIT COMPARISON

2.1 Prevention of COVID-19 hospitalisations

For 100 000 people with low exposure risk[a]

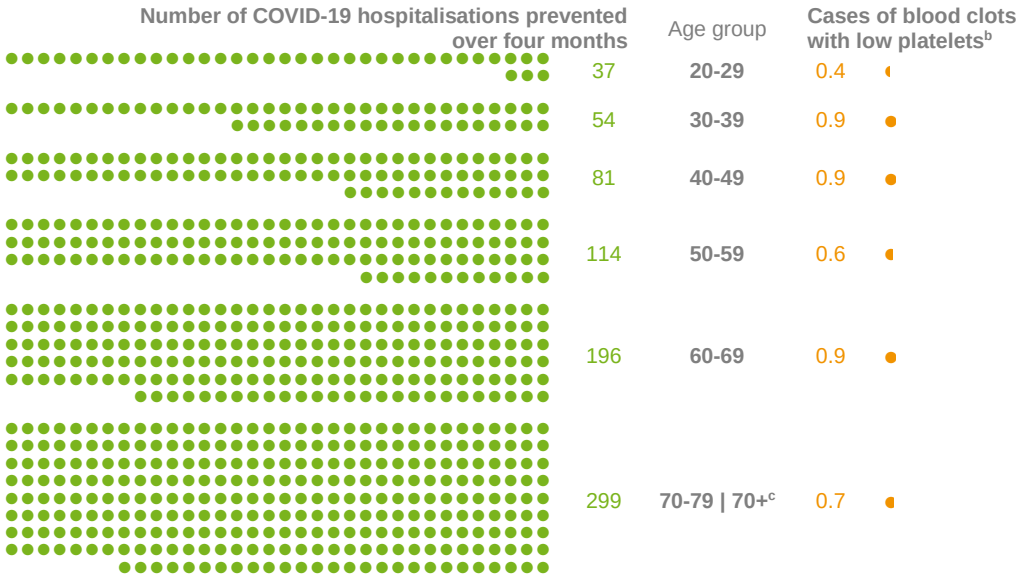


[a] *COVID-19 incidence of 55 per 100 000 people per month (EU September 2020).*

[b] *Increased with 20% to attenuate possible underreporting (see method section for details).*

[c] *Cases of blood clots with low platelets data are available aggregated for 70+, while the EMA data are available for 70-79 and 80+. We conservatively chose to compare with the 70-79 age group as the benefits for 80+ are higher (see method section for details).*

For 100 000 people with medium exposure risk[a]

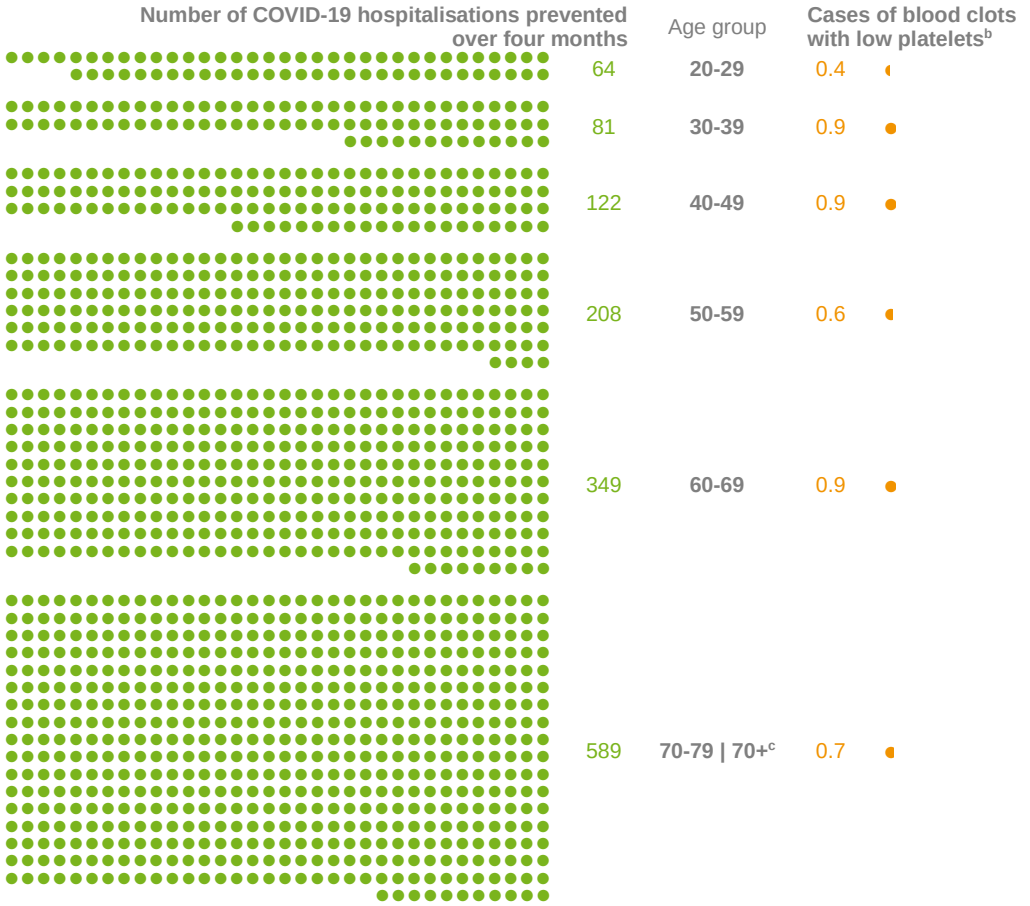


[a] *COVID-19 incidence of 401 per 100 000 people per month (EU March 2021).*

[b] *Increased with 20% to attenuate possible underreporting (see method section for details).*

[c] *Cases of blood clots with low platelets data are available aggregated for 70+, while the EMA data are available for 70-79 and 80+. We conservatively chose to compare with the 70-79 age group as the benefits for 80+ are higher (see method section for details).*

For 100 000 people with high exposure risk[a]



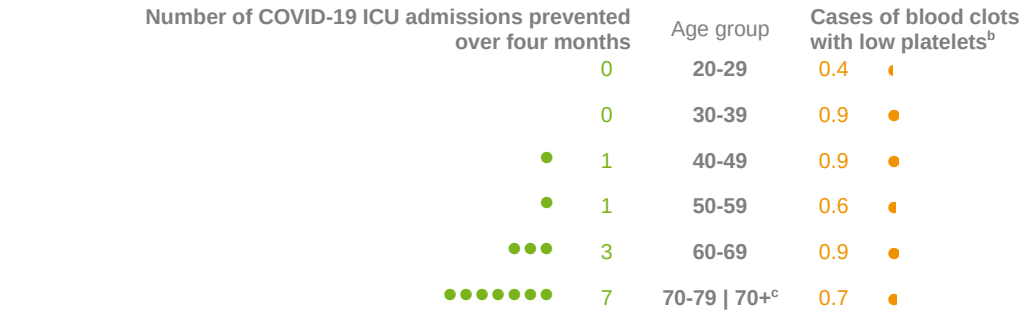
[a] *COVID-19 incidence of 886 per 100 000 people per month (EU January 2021).*

[b] *Increased with 20% to attenuate possible underreporting (see method section for details).*

[c] *Cases of blood clots with low platelets data are available aggregated for 70+, while the EMA data are available for 70-79 and 80+. We conservatively chose to compare with the 70-79 age group as the benefits for 80+ are higher (see method section for details).*

2.2 Prevention of COVID-19 ICU admissions

For 100 000 people with low exposure risk[a]

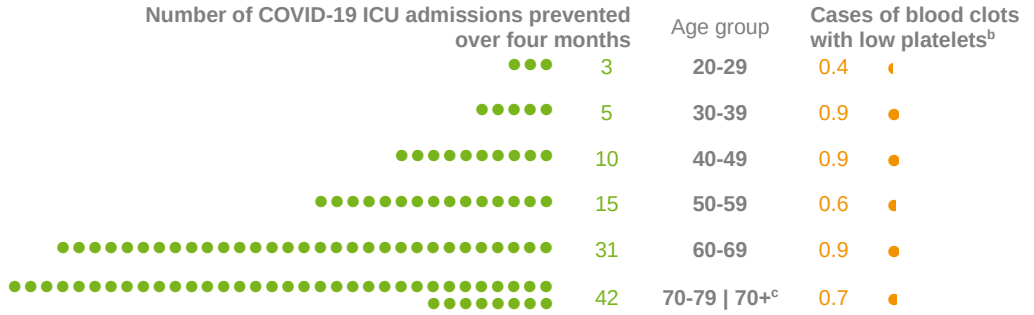


[a] *COVID-19 incidence of 55 per 100 000 people per month (EU September 2020).*

[b] *Increased with 20% to attenuate possible underreporting (see method section for details).*

[c] *Cases of blood clots with low platelets data are available aggregated for 70+, while the EMA data are available for 70-79 and 80+. We conservatively chose to compare with the 70-79 age group as the benefits for 80+ are higher (see method section for details).*

For 100 000 people with medium exposure risk[a]

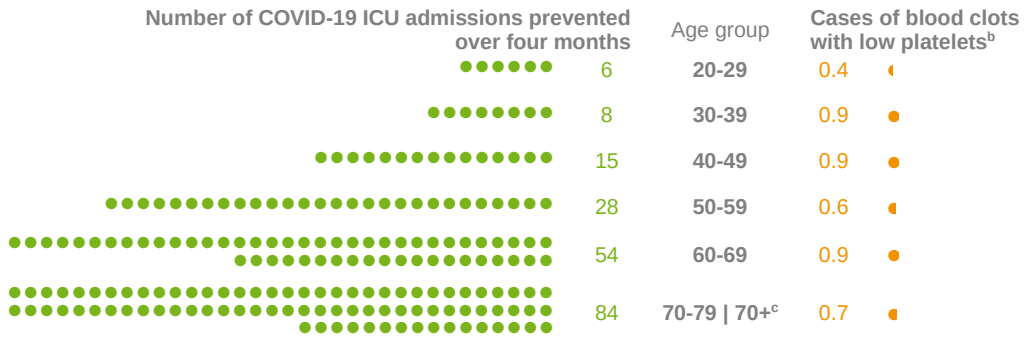


[a] *COVID-19 incidence of 401 per 100 000 people per month (EU March 2021).*

[b] *Increased with 20% to attenuate possible underreporting (see method section for details).*

[c] *Cases of blood clots with low platelets data are available aggregated for 70+, while the EMA data are available for 70-79 and 80+. We conservatively chose to compare with the 70-79 age group as the benefits for 80+ are higher (see method section for details).*

For 100 000 people with high exposure risk[a]



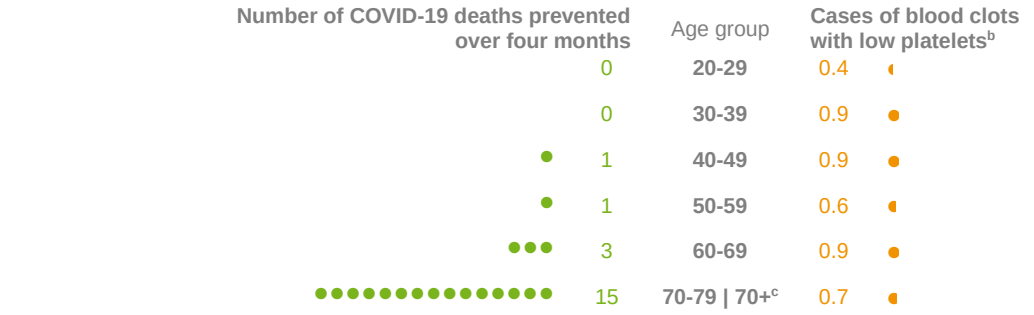
[a] *COVID-19 incidence of 886 per 100 000 people per month (EU January 2021).*

[b] *Increased with 20% to attenuate possible underreporting (see method section for details).*

[c] *Cases of blood clots with low platelets data are available aggregated for 70+, while the EMA data are available for 70-79 and 80+. We conservatively chose to compare with the 70-79 age group as the benefits for 80+ are higher (see method section for details).*

2.3 Prevention of COVID-19 deaths

For 100 000 people with low exposure risk[a]

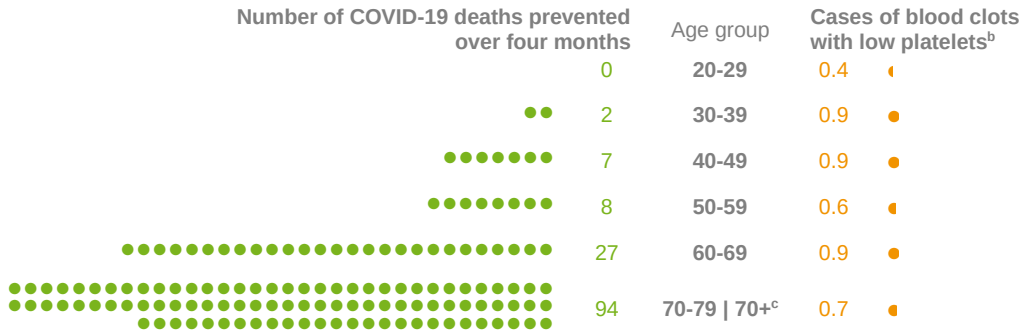


[a] *COVID-19 incidence of 55 per 100 000 people per month (EU September 2020).*

[b] *Increased with 20% to attenuate possible underreporting (see method section for details).*

[c] *Cases of blood clots with low platelets data are available aggregated for 70+, while the EMA data are available for 70-79 and 80+. We conservatively chose to compare with the 70-79 age group as the benefits for 80+ are higher (see method section for details).*

For 100 000 people with medium exposure risk[a]

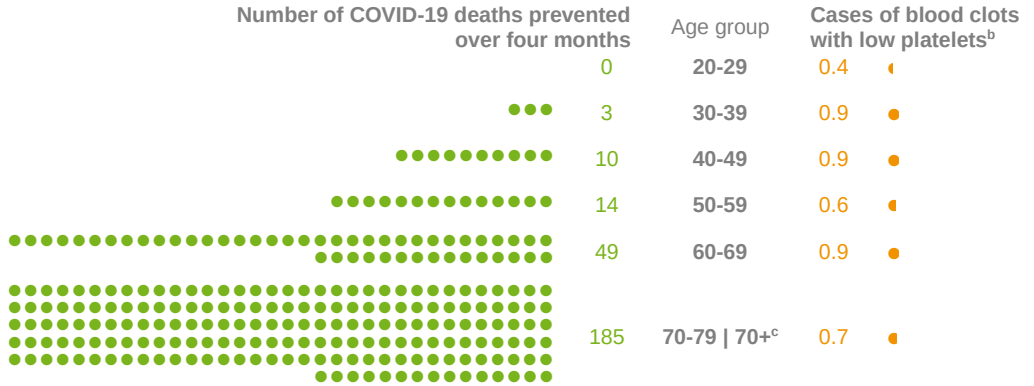


[a] *COVID-19 incidence of 401 per 100 000 people per month (EU March 2021).*

[b] *Increased with 20% to attenuate possible underreporting (see method section for details).*

[c] *Cases of blood clots with low platelets data are available aggregated for 70+, while the EMA data are available for 70-79 and 80+. We conservatively chose to compare with the 70-79 age group as the benefits for 80+ are higher (see method section for details).*

For 100 000 people with high exposure risk[a]



[a] *COVID-19 incidence of 886 per 100 000 people per month (EU January 2021).*

[b] *Increased with 20% to attenuate possible underreporting (see method section for details).*

[c] *Cases of blood clots with low platelets data are available aggregated for 70+, while the EMA data are available for 70-79 and 80+. We conservatively chose to compare with the 70-79 age group as the benefits for 80+ are higher (see method section for details).*

3 METHOD

3.1 EMA risk benefit contextualisation for thrombosis with thrombocytopenia syndrome

EMA published a risk benefit contextualisation of the Vaxzevria™ vaccine, focusing on the risk of thrombosis with thrombocytopenia syndrome (TTS), at the end of April 2021. The underlying risk benefit contextualisation, version of 21-04-2021, was put at the disposal of EU member states for further use. An adapted version of 23-04-2021 was used for final publication by EMA and is used for our analysis as well.

Details of the data and assumptions of this contextualisation are available in Use of Vaxzevria to prevent COVID-19 - Article-5(3) procedure: Assessment report.

We reuse the EU estimates on hospitalisation, ICU and death, provided by EMA for conducting the contextualisation, adjusting them to the vaccine efficacy for the Johnson & Johnson vaccine.

Vaccine efficacy for the Johnson & Johnson vaccine is retrieved from EMA: https://www.ema.europa.eu/en/medicines/human/EPAR/covid-19-vaccine-janssen.

We assume 85% vaccine efficacy (rounded to nearest integer) for all three possible benefits, corresponding to prevention of hospitalisation, ICU admission or death following severe-critical COVID-19 as reported in the analysis, excluding participants who were RT-PCR–positive between days 1 and 28 after the administration of vaccine or placebo.

The analysis is performed for three different epidemiological scenarios, similar to the EMA risk benefit contextualisation of TTS after Vaxzevria™ vaccine:

Low infection rate

Using virus circulation in the EU of September 2020: 55 per 100 000 people.

Medium infection rate

Using virus circulation in the EU of March 2021: 401 per 100 000 people.

High infection rate

Using virus circulation in the EU of January 2021: 886 per 100 000 people.

3.2 Thrombosis with thrombocytopenia syndrome (TTS)

USA Centres for Disease Control and Prevention (CDC) summarised reported TTS events following vaccination with the Johnson & Johnson vaccine on May 24 in unpublished preliminary results, following a public reporting on May 12[a]. Due to the severe time limit for this analysis, we could not request additional information to CDC. The adaptions necessary to be able to compare TTS with the EMA calculated benefits are described in this section.

The number of TTS events per age group is shown in column 1 and 2 of Table 1. The data include unfortunately only the total number of vaccinated with the Johnson & Johnson vaccine (10 323 402). For the May 24 data, we extrapolated the total number of vaccinated with the Johnson & Johnson vaccine to each age group, using the proportion of vaccinated per age group on May 12 (see column 3 of Table 1).

The May 12 reported data on number of vaccinated with the Johnson & Johnson vaccine aggregate these in 60+ age group. As we have the TTS for age groups 60-69 and 70+, we partitioned the total number of vaccinated in the 60+ age group to the two age groups 60-69 and 70+, using the US Cencus population data of 2019 (latest available). We assume that people aged 60-69 and 70+ are vaccinated proportionally to their population proportion.

[a] https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/07-COVID-Shimabukuro-508.pdf

We believe the impact of these choices is limited as there is no indication the US vaccination strategy changed drastically in two weeks' time between age groups.

The May 12 reported data on number of vaccinated with the Johnson & Johnson vaccine youngest age group includes 18 and 19 years old as well. Since the number of vaccinated with the Johnson & Johnson vaccine include these ages as well, we could not extract them. We use this 18-29 age group to compare with the 20-29 age group in the EMA contextualisation. We believe this choice is conservative as the benefits concern a smaller number of people.

The resulting TTS per 100 000 vaccinated with the Johnson & Johnson vaccine are found column 4 of Table 1.

Similarly to the EMA contextualisation of the VaxzevriaTM vaccine, we assume there currently is an underreporting of TTS cases. In the original EMA contextualisation, this was calculated as:

- TTS onset day 1 to 7: 0%
- TTS onset day 8 to 14: +20%
- TTS onset from day 15 onwards: +50%

We adapted the underreporting as all TTS events reported seem to have occurred within 15 days of vaccination, and the TTS event onset is not reported by age group: to attenuate for underreporting, we add 20% of events (see column 5 in Table 1).

Table 1 – TTS events by age group

Age group	TTS events reported May 24	Number of people vaccinated with Johnson & Johnson vaccine	TTS events per 100 000	TTS events per 100 000 (20% added for underreporting)
20-29	5	1 603 854	0.3	0.4
30-39	12	1 622 160	0.7	0.9
40-49	13	1 796 272	0.7	0.9
50-59	12	2 347 410	0.5	0.6
60-69	12	1 527 511	0.8	0.9
70+	8	1 426 195	0.6	0.7