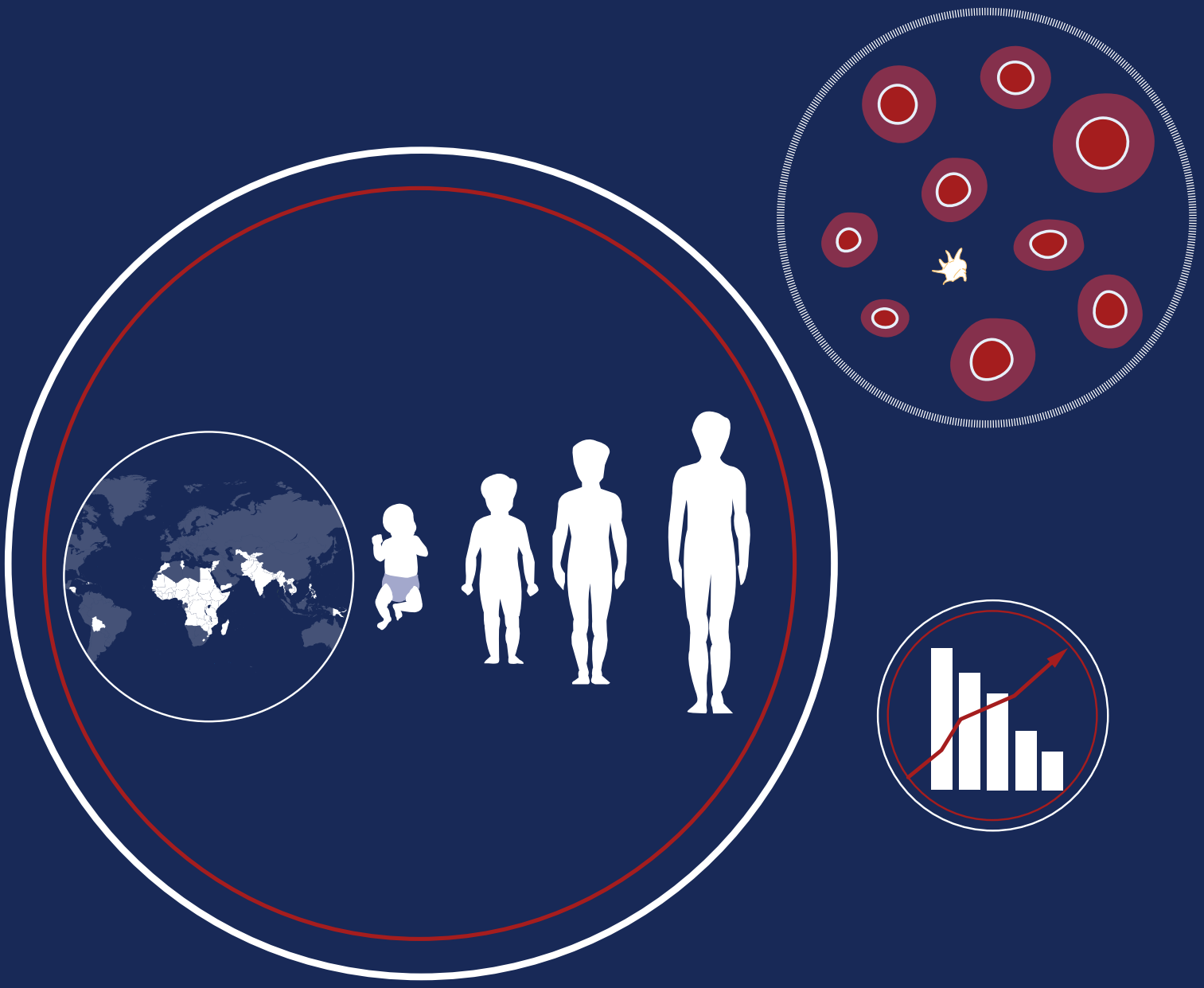
Protocol on estimation of thrombocytopenia background rates in children aged 5 months to <15 years

in low- and middle-income countries



World Health Organization

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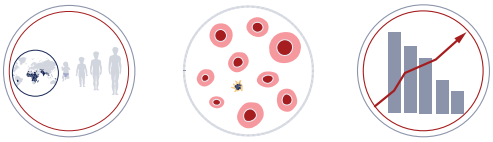

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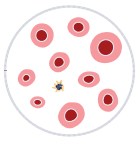
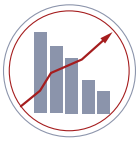
Declaration of interest

Before commissioning P95 to write the protocol, as part of WHO policy, written disclosures of potential conflicts of interest that might affect, or might reasonably be perceived to affect, objectivity and independence in relation to the protocol were reviewed. Additionally, all experts involved in the development and peer reviewers submitted a WHO declaration of interest, disclosing potential conflicts of interest. WHO reviewed each of the declarations and concluded that none could give rise to potential or reasonably perceived conflict of interest.

Abbreviations

AESI	adverse event of special interest
GDPR	General Data Protection Regulation
LMICs	low- and middle-income countries
MMR vaccine	measles–mumps–rubella vaccine
WHO	World Health Organization

1. Synopsis

Full title of study

Estimation of thrombocytopenia background rates in children aged 5 months to <15 years in low- and middle-income countries.

Background and rationale

Background rates of possible adverse effects are crucial to monitoring vaccine safety because they help separate potential safety signals following vaccination from events that are temporally associated with but not caused by vaccination.

Thrombocytopenia, a condition in which the number of platelets in the blood is abnormally low *(1)*, is an adverse event of special interest (AESI) because of its known and theoretical association with the measles–mumps–rubella (MMR) vaccine *(2–5)*. Vaccines are designed to induce immune responses that mimic infections to produce immunological protection. It is theoretically possible that vaccines other than the MMR vaccine could also trigger thrombocytopenia. Two studies have implicated (showed minimal risk for) two SARS-CoV-2 vaccines in the development of immune thrombocytopenia *(6–8)*. Clinically apparent thrombocytopenia following immunization is rare: the incidence rate has previously been estimated to be in the range of 0.1–4.0 cases per 100 000 children vaccinated with the MMR vaccine in Europe and north America *(2–5, 9–11)*.

Current evidence remains insufficient to definitively establish a link between vaccines other than MMR and thrombocytopenia. To address this gap, a multicountry health facility-based study with high participation from low- and middle-income countries (LMICs) that uses a common protocol and standardized procedures can produce reliable estimates of the occurrence of rare AESIs such as thrombocytopenia *(12)*. The Global Vaccine Safety Blueprint reiterates the need for such multicountry studies *(13)*.

Two recently developed vaccines – the Malaria R21 vaccine (targeting children aged 5–36 months) and the dengue vaccine (targeting people aged over 3 years) – are anticipated to be introduced in most LMICs within the next few years. Establishing background rates of thrombocytopenia before introducing these vaccines will be instrumental in establishing a baseline against which to evaluate the occurrence of adverse events following vaccine introduction.

Objectives

- To estimate the annual background rates of thrombocytopenia in children aged 5 months to <15 years.
- To estimate the annual rate of thrombocytopenia following vaccination (with any vaccine) in children aged 5 months to <15 years.

Study design

This is a multisite prospective observational study conducted in selected sentinel sites in LMICs. A prospective study is the recommended design to collect good-quality data on AESIs because medical records are often not available in electronic format and physical archives are not always accessible in LMICs. Cases of thrombocytopenia will be ascertained in participating health facilities. Denominators (population living in the catchment area of the health facility) for the incidence rate calculation will be estimated using the most recent census data.

This study design is selected as the most feasible for background rate estimation in LMICs because the use of census data for the denominator means it does not require prospective follow-up of a large population.

Study period

6–12 months.

Study population and catchment area

The study population is children and adolescents aged 5 months to <15 years residing in the catchment area of the health facility.

The catchment population is the size of the total population served by the health facility. The catchment area is the geographical area from which the users of the health facility are drawn. In summary, the catchment population can be estimated as follows:

- The geographical coordinates of the health facility are identified. The service area of the health facility is determined, which may be the government administrative region that the health facility is expected to serve.
- The smallest administrative units that the service area can be subdivided into are identified. The population for each small administrative area is derived from the most recent national population census and projected forward using district-level intercensal growth rates.
- Geographic information systems software is used to identify the centroid of the small administrative areas. The travel time from the centroid to the primary road and from the primary road to the health facility is calculated – this represents the average travel time from each home in the small administrative area to the health facility.
- The catchment area is initially limited to an area within a 60-minute drive of the health facility. Travel time is then divided into three zones of driving time – 0–20 minutes, 20–40 minutes and 40–60 minutes.
- The travel zones are assigned different weights to account for distance decay.
- The total person-years observed in a catchment area (e.g. over one year) are estimated by multiplying the population estimates of each of the small administrative areas within the health facility catchment area with the respective travel time weights and summing them up.

Study outcomes and case identification

Thrombocytopenia is defined using the Brighton Collaboration case definition *(1)* and studied among children aged 5 months to <15 years in preparation for the introduction of malaria and dengue vaccines.

Recent immunization (within 42 days) and clinical history are recorded to determine whether the participant has been vaccinated recently.

Data sources

Case data are identified and recorded by the study team in the participating health facilities.

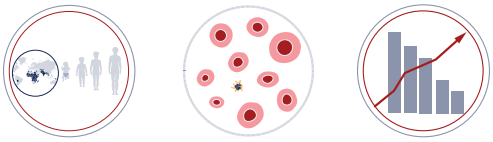
Population census data are requested from the respective national statistical offices.

Sample size

Sample sizes were determined with the aim to estimate the rate of thrombocytopenia with a prespecified precision.

Data analysis

The incidence rate of all-cause thrombocytopenia and thrombocytopenia following vaccination is calculated as the total number of identified cases divided by the size of the catchment population per 100 000 person-years. Annual rates (with corresponding 95% confidence intervals) are calculated. All rates are additionally stratified by age group, site and country.



Ethics

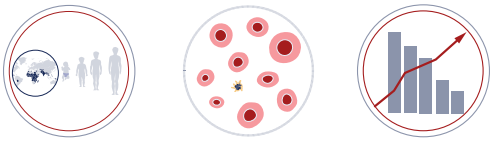
The study will be conducted according to the International Ethical Guidelines for Health-related Research involving Humans *(14)*, under the principles of the Declaration of Helsinki *(15)* and considering local legislation on medical research in humans and data sharing from clinical records beyond national or administrative borders.

Informed consent will be required from all participants.

All parties will ensure protection of personal data and will not include names or other identifying information (e.g. date of birth, address) on any study forms, reports or publications or in any other disclosures, except where required by law. Local data protection and privacy regulations will be observed in capturing, forwarding, processing and storing data.

This protocol serves a dual purpose. Countries can implement it independently without World Health Organization (WHO) involvement or use it as a master protocol supported by WHO for implementation.

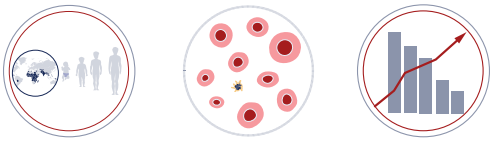
This master protocol has been approved by the WHO Research Ethics Review Committee. Each participating site will be responsible for submission of the study protocol and any amendment to the respective local, national or independent ethics committees and/or institutional review boards according to local requirements.



2. Use of this protocol

This is a master protocol approved by the WHO Research Ethics Review Committee on 20 May 2025. The protocol will be used by study sites that will submit a protocol to their national ethics review committees. The only country-specific changes that should be made are changes needed to facilitate translation into the local language and changes advised by the national ethics review committee.

Amended site-specific protocols developed for implementation in countries based on this WHO master protocol must be approved by the WHO Research Ethics Review Committee before implementation. Any third party that uses or follows this protocol does so at its sole discretion, and WHO will not have any responsibility or liability of any kind arising from or in connection with any use or following of this protocol by any third parties and/or the conduct of any studies by third parties that use or follow the protocol. Studies conducted by third parties pursuant to the protocol cannot be considered WHO studies, and third parties using or following this protocol for their studies will not label, characterize or otherwise represent such studies as “WHO studies”. All necessary and/or appropriate approval(s) at the local and/or national level(s) should be obtained before starting any such study.



3. Background and rationale

An adverse event of special interest (AESI) is a prespecified medically significant event that has the potential to be causally associated with a vaccine product and that needs to be monitored carefully and confirmed by further special studies. AESIs can have multiple potential causes and can occur independently from receipt of vaccine products. It is important to understand the rate of occurrence of AESIs before vaccine introduction, so there is a frame of reference with which to compare the rates of AESIs to identify any rate increase as a potential safety concern.

This master protocol has been developed to support the implementation of a study in which the primary objective is estimation of the background rate of thrombocytopenia in children aged 5 months to <15 years in low- and middle-income countries.

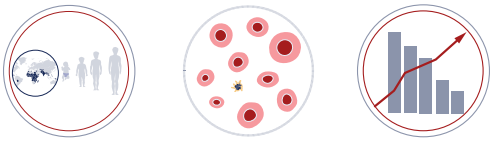
Thrombocytopenia is a condition in which the number of platelets in the blood is abnormally low *(1)*. There are three main pathogenic mechanisms that can lead to thrombocytopenia – insufficient production, abnormal distribution and excessive destruction of platelets. Excessive destruction can be caused by microangiopathy, hereditary platelet abnormalities or immunological mechanisms. The pathogenesis of thrombocytopenia following wild virus infections and immunizations is not fully understood, but it is thought to be complex, with causes including viral destruction of megakaryocytes and platelets, immunostimulation and antigenic mimicry between virus and platelet antigens *(1, 16)*.

Thrombocytopenia is an AESI because of its known association with the measles–mumps–rubella (MMR) vaccine in children *(2–5)*. The risk of thrombocytopenia after vaccination with vaccines other than MMR is unknown. Vaccines are designed to induce immune responses that mimic infections to produce immunological protection, and it is theoretically possible that vaccines other than MMR could trigger thrombocytopenia. Two studies have implicated (showed minimal risk) two SARS-CoV-2 vaccines in developing immune thrombocytopenia *(6–8)*. Clinically apparent thrombocytopenia following immunization is rare: the incidence rate has previously been estimated to be in the range of 0.1–4.0 cases per 100 000 children vaccinated with the MMR vaccine *(2–5, 9–11)*.

Current evidence remains insufficient to definitively establish a link between vaccines other than MMR and thrombocytopenia. To address this gap, a multicountry health facility-based study with high participation from LMICs that uses a common protocol and standardized procedures can produce reliable estimates of the occurrence of rare AESIs such as thrombocytopenia *(12)*. Previously, multicountry studies have been used to investigate the association between measles vaccines and aseptic meningitis and idiopathic thrombocytopenic purpura *(12, 17)*, and the association between rotavirus vaccines and intussusception *(18)*. The WHO Global Vaccine Safety Blueprint reiterates the need for pooled safety data from extensive multicountry surveillance studies to understand complex vaccine safety issues better and improve pharmacovigilance efforts in LMICs *(13, 19)*.

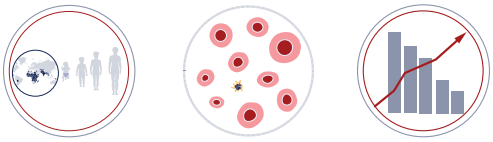
Two recently developed vaccines – the Malaria R21 vaccine (targeting children aged 5–36 months) and the dengue vaccine (targeting people aged over 3 years) – are anticipated to be introduced in most LMICs within the next few years. Establishing background rates of thrombocytopenia in the targeted age groups before introducing these vaccines will be instrumental in establishing a baseline against which to evaluate the occurrence of adverse events following vaccine introduction.

The primary objective of this project is to prospectively generate evidence on background rates of thrombocytopenia before the introduction of the malaria and dengue vaccines. As a secondary objective, the incidence rate of thrombocytopenia following vaccination among children aged 5 months to <15 years in multiple LMICs *(20)* will be measured.



4. Objectives

- To estimate the annual background rate of thrombocytopenia from all causes among children aged 5 months to <15 years.
- To estimate the annual rate of thrombocytopenia following vaccination with any vaccine in children aged 5 months to <15 years.



5. Methodology

5.1 Study setting

The study will be conducted in LMICs, defined according to the World Bank classification *(20)*. In each country, one or more secondary or tertiary health facilities will be selected. Ideally, the selected health facility will be a tertiary care hospital with adequate diagnostic facilities and specialists for care of people with thrombocytopenia. The participating health facilities will be selected according to data collected in the health facility screening questionnaire (see Annex 1).

5.2 Study design

This will be a multisite prospective observational study conducted in selected sentinel sites in LMICs. A prospective study is the recommended design to collect good-quality AESI data because electronic medical records are often not available and physical archives are not always accessible in LMICs. Cases will be ascertained in participating facilities. Denominators will be derived from the health facility catchment population. This study design is selected as the most feasible for background rate estimation in LMICs because it does not require prospective follow-up of a large population.

The countries and sites to be included in the study will be determined by WHO Headquarters and regional and country offices. The WHO Pharmacovigilance team will coordinate the study. Initially, WHO will support one or two countries as a pilot. Based on the lessons learned, WHO will expand support to other countries that express an interest.

5.3 Study population

5.3.1 Source population

The source population (also known as the catchment population) will comprise people of aged 5 months to <15 years residing in the health facility catchment area that gives rise to the cases of thrombocytopenia. The establishment of the catchment population is outlined in Section 5.5. Study participants will comprise of all people with suspected thrombocytopenia pending confirmation for thrombocytopenia using the Brighton Collaboration of case definition *(1)* (see Annex 5). Screening for suspected thrombocytopenia and identification of thrombocytopenia is outlined in Section 5.7.3.

5.3.2 Inclusion criteria

- The potential participant is a resident of the catchment area of the participating health facility at the time of case identification: a resident is defined as a person who has lived in the catchment area for at least one month and intends to live within the catchment area for a minimum of three months.
- The potential participant is aged 5 months to <15 years.
- The potential participant is admitted to the participating health facility with a confirmed diagnosis of thrombocytopenia or meeting the screening criteria suggestive of suspected thrombocytopenia.
- Informed assent is gained from the study participant, and informed consent is gained from their parent or legally authorized representative (see Annex 2).

5.3.3 Exclusion criteria

The inclusion criteria are specific and there is no need for exclusion criteria.

A child will be excluded if they or their parent or legally authorized representative cannot consent due to barriers such as critical illness or language. The number of children not consenting and the reasons for this will be noted.

5.3.4 Study sites

In each country, one or more study sites meeting the site selection criteria will be selected. Each participating health facility will have a well-defined catchment area. Site study teams will be based in the health facility led by the site principal investigator.

5.3.5 Country and site selection criteria

Country selection

- The country is a LMIC according to the World Bank classification *(20)*.
- The country has a functional national pharmacovigilance system willing to strengthen its capacity to monitor the safety of vaccines. The WHO Global Benchmarking Tool *(21)* will be used to assess the functionality of national regulatory authorities. The national pharmacovigilance system should be at a minimum of maturity level 2.

Preliminary health facility identification

- The health facility is in a region where census data are available, and the census was conducted no more than 10 years before the start of the study. The census data will be used to estimate the population within the catchment area.
- The health facility has a laboratory capable of conducting peripheral blood smear tests and complete blood count.
- The health facility has easily accessible medical records (electronic and/or paper) to supplement prospectively collected data.
- The health facility has qualified personnel and specialists, such as a haematologist.
- The health facility has a large enough number of annual admissions to estimate the incidence rate of thrombocytopenia with reasonable precision (on the basis of estimated person-years for people admitted for any disease or medical condition; see Section 5.8.1).

Facilities that fulfil the initial screening criteria will proceed to complete the health facility screening questionnaire (see Annex 1). The information gathered from the questionnaire will be used to evaluate the operational and diagnostic capabilities of the health facility. Questions cover the type of health facility (public or private), the qualification of staff to identify suspected and confirmed cases of thrombocytopenia and complete case report forms, laboratory testing capabilities (e.g. ability to perform peripheral blood smear tests), and the mode of data collection and record-keeping (paper or electronic). The WHO regional office, in liaison with the WHO country office, will consult the ministry of health or national regulatory authority regarding the eligibility criteria of choosing participating sites.

5.4 Study period

The specific start and end dates of the study for each site will be decided by the site study team and the WHO Pharmacovigilance team.

5.5 Catchment area and population size

The catchment area refers to the geographical region where the people using the health facility live. The catchment population is the size of the population living in the catchment area that the health facility serves. The size of the catchment population is estimated as follows:

1 Identify and assign geographical coordinates (latitude and longitude) to the participating health facility.

2 Determine the service area of the participating health facility. In most LMICs, primary health facilities are assigned administrative regions that they are expected to serve. The term “service area” is used to refer to this assigned region.

3 Identify the smallest administrative units that the service area can be subdivided into (e.g. sublocations). These boundaries can be obtained from the national statistical office.

4 Derive the population for each small administrative area from the most contemporary national population census and project it forward using district-level intercensal growth rates.

5 A typical census report provides mid-year and year-end population estimates. If multiple estimates are available, use the mid-year estimate.

6 Use geographic information systems software to identify the centroid of the small administrative areas. Calculate the travel time from the centroid to the primary road and from the primary road to the health facility – this represents the average travel time from each home in the small administrative area to the health facility.

7 Limit the catchment area initially to an area within a 60-minute drive of the health facility. This is the time it takes to travel from the furthest centroid in the catchment area to the health facility.

8 Divide the time into three zones of driving time – 0–20 minutes, 20–40 minutes and 40–60 minutes.

9 Assign the travel zones different weights based on a Gaussian function to account for distance decay *(22, 23)*.

10 Estimate the total person-years observed in a catchment area (e.g. over one year) by multiplying the population estimates of each of the small administrative areas within the catchment area with the respective travel time weights and summing them.

An enhanced two-step floating catchment area method *(24)* is used to measure and visualize spatial accessibility of the health facility.

5.6 Study outcomes

5.6.1 Thrombocytopenia

The primary outcome is thrombocytopenia, based on the Brighton Collaboration case definition *(1)* (see Annex 5). Information gathered using the health facility screening questionnaire (see Annex 1) is used to determine the level of diagnostic certainty that will be used to identify thrombocytopenia.

5.6.2 Classification of thrombocytopenia

Recent vaccination with any vaccine and clinical history are recorded (see Annex 6) to determine whether the participant has been vaccinated recently (≤6 weeks). This information is used to address the secondary objective to calculate the incidence rate of thrombocytopenia following vaccination with any vaccine and adjust for coexisting infections that can cause thrombocytopenia (e.g. malaria, dengue) in the analysis.

Only documented evidence of recent vaccination history is used. Recent clinical history on viral, bacterial or parasitic infection is obtained from medical records if the participant presented to the participating health facility for treatment. Otherwise, self-reported clinical history is recorded. Participants will be asked about vaccination cards, vaccination reminders, and adherence to specific vaccine schedules due for their age group according to national vaccination programmes.

Questions about recent vaccination include whether the participant has been vaccinated recently, the date of vaccination, the number of doses received, the disease targeted by the vaccine, and the name of the vaccine. Questions about recent clinical history include whether the participant has been ill recently with diarrhoeal or respiratory illness (including influenza), date of illness, where they sought treatment and results from relevant laboratory tests.

5.7 Study flow: case identification and data collection

5.7.1 Recruitment

Recruitment of study participants will take place at the health facility. People arriving at the health facility who fulfil the screening criteria for thrombocytopenia will be informed, through their parents or legally authorized representatives, about the study. The study team will explain all the relevant information regarding the study. The potential participant and their parent or legally authorized representative will be given an opportunity to discuss the material and ask questions.

The parent or guardian of the potential participant will be required to read the full consent form or receive a full oral explanation in an appropriate language. They will be asked individually by the study team whether they understand all parts of the consent and will be given another opportunity to ask any questions and seek clarification. Older children aged over 8 years will be asked to provide assent, and their parents or legally authorized representative asked to sign the informed consent form or to place a thumbprint on the informed consent form in the presence of an impartial witness. Detailed study procedures will be described in specific manuals and standard operating procedures.

An anonymized record will be kept of the number of children or adolescents (with age and sex) who did not consent or whose parents did not consent. This number will help in the interpretation of results, because refusal to participate can introduce potential bias.

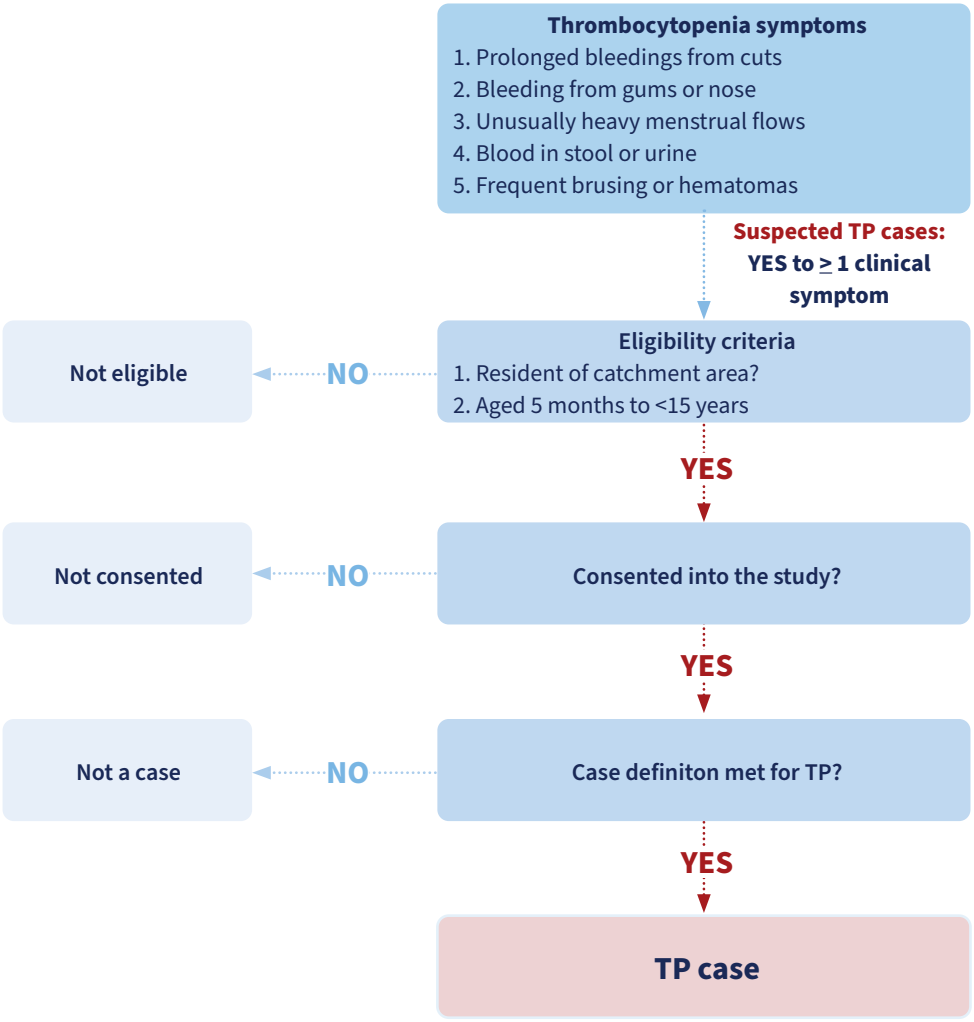
5.7.2 Study enrolment and withdrawal

People who meet the inclusion criteria in Section 5.3.2 will be enrolled by study staff, who will then start the process of case identification. Research staff will be trained to approach potential participants and their families for consent only after the doctor has seen them and their medical situation is stable, ensuring there is no pressure to participate. Eligible potential participants will be approached in consecutive order, although some may be approached later due to acute presentations. Study procedures will prioritize immediate care over research and can be paused if medical needs arise. Data will be extracted from existing records without additional procedures. The staff member obtaining consent will not be the same staff member treating the participant and will ensure participation in the study does not affect the quality of care.

Potential participants will have sufficient time to ask questions and make decisions with staff trained to observe and address any signs of pressure. Potential participants will have the right to withdraw from the study for any reason at any time. The age and sex of people who choose not to consent or who are not able to comply with the required follow-up will be recorded at the study sites at the point of enrolment. These data will be de-identified and stored securely to protect privacy.

5.7.3 Screening for suspected cases of AESI

Figure 1. Flow diagram of screening and recruiting participants



Before confirming thrombocytopenia, a screening criterion will be used to identify people presenting to the health facility with suspected thrombocytopenia. The screening criteria for a person with suspected thrombocytopenia will be any of the following symptoms:

- prolonged bleeding from cuts;
- bleeding from gums or nose;
- unusually heavy menstrual flow in older children;
- blood in stool or urine;
- frequent bruising or haematomas.

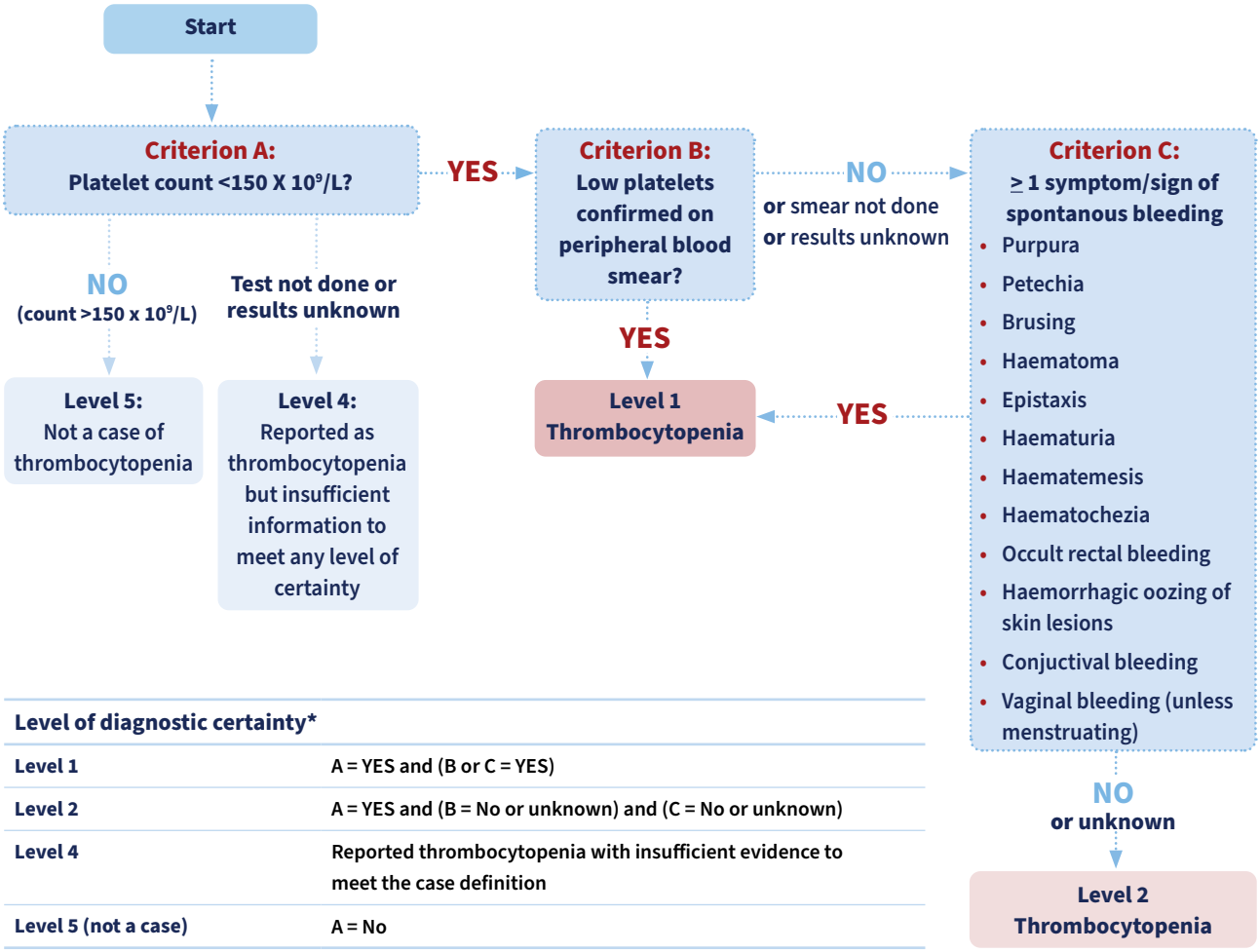
5.7.4 Thrombocytopenia case identification

The Brighton Collaboration case definitions for thrombocytopenia based on three levels of diagnostic certainty are provided in Annex 5. The level of diagnostic certainty to be used depends on the diagnostic capabilities of the participating health facility, which will be assessed using the health facility screening questionnaire (see Annex 1). An assessment will be conducted to evaluate the diagnostic capability of each health facility under consideration. Events that do not meet the case definition will be classified as either *(1)*:

- reported as thrombocytopenia with insufficient evidence to meet any level of certainty;
- not thrombocytopenia.

People with suspected thrombocytopenia will be approached by study staff for consent before ascertaining the case as thrombocytopenia according to the Brighton Collaboration case definitions.

Figure 2. Algorithm for ascertaining a case as thrombocytopenia (Brighton Collaboration case definition)



Level of diagnostic certainty*	
Level 1	A = YES and (B or C = YES)
Level 2	A = YES and (B = No or unknown) and (C = No or unknown)
Level 4	Reported thrombocytopenia with insufficient evidence to meet the case definition
Level 5 (not a case)	A = No

* Refer to case definitions based on the different levels of certainty in the protocol annex

Source: Law B. Thrombocytopenia: case definition pictorial algorithm. Zenodo; 2021 (https://doi.org/10.5281/zenodo.7035786, accessed 22 May 2025).

Figure 2 shows how different levels of certainty of the diagnosis of thrombocytopenia are derived. Level 1 is the highest certainty and requires a low platelet count (<150 × 10^9/L) (criterion A) plus either a blood smear confirmation (criterion B) or bleeding symptoms (criterion C). Level 4 denotes cases with insufficient information (missing platelet count). Level 5 confirms people who do not have thrombocytopenia (normal platelet count). Level 1 cases are primary, and level 2 is moderate certainty.

5.7.5 Data sources

This observational study will ascertain cases in the participating health facility. The at-risk population (denominators) will be estimated using recent census data. Once the catchment area has been identified, a data request for population counts in small administrative areas and boundaries will be sent to the country's statistical office. These denominator data will be used to estimate the person-years of observation in incidence rate calculations.

An alternative source of denominator data are health and demographic surveillance systems, which closely monitor population groups over time and therefore have accurate estimates of person-years. Where possible, if the identified catchment area falls within the geographical area covered by the health and demographic surveillance systems, a data request is sent to the health and demographic surveillance systems site for person-year data.

5.7.6 Data collection and generation

Upon meeting the inclusion criteria, data will be collected by study staff using standardized tools (see Annex 6). The study data managers will use manual and automated data cleaning processes to detect and flag out-of-range or anomalous data. Methods of data collection will be consistent between study settings. Additional information on data management is described in Section 5.9. Harmonized data collection procedures will be described in a specific manual of study procedures.

Thrombocytopenia data collection

The following information will be collected and used to confirm thrombocytopenia cases using one of the three levels of diagnostic certainty (see Annex 5):

- systematic evaluation or clinical description of signs and symptoms of spontaneous bleeding required to meet the case definition for thrombocytopenia;
- laboratory examinations, including complete blood count and peripheral blood smear;
- method of measurement (e.g. used for platelet count) (automated haematology);
- dates of admission, physical examinations and laboratory tests;
- signs or symptoms of infection and presence of parasites or viruses in blood smear (if available as part of routine medical care).

Six-week clinical and vaccination history data collection

The following vaccination history data will be collected (see Annex 6):

- history of thrombocytopenia from an identified or unknown cause;
- vaccine(s) received in the past six weeks.

5.7.7 Case report form completion

As much information as possible will be abstracted from routinely collected medical records at admission and filled in case report forms. Case adjudication will be done by a physician, paediatrician or haematologist. Any additional information required but not routinely collected by the health facility will be obtained directly from the participant by the study team.

5.8 Statistical methods

5.8.1 Sample size calculation

Sample sizes will be determined based on the desired level of precision of the rate. The sample size required to estimate the incidence rate of thrombocytopenia (e.g. in one year) with a given level of precision for each site is as follows *(25)*:

$$n = \frac{u * Z^2}{e^2}$$

where:

n is the required person-years;

u is the expected rate of thrombocytopenia (annual incidence is estimated to be 4.2–17.1 cases per 100 000 person-years in children aged <15 years) *(26–28)*;

e is the precision (half-width of the 95% confidence interval);

Z is the critical value for the 95% confidence level.

Table 1. Sample size considerations for thrombocytopenia

	Expected AESI rate (per 100 000 person-years)				
Precision (per 100 000 person-years)	**4**	**8**	**12**	**16**	**17**
2.0	384 160	768 320	1 152 480	1 440 600	1 632 680
3.0	170 738	341 476	512 214	640 267	725 636
4.0	96 040	192 080	288 120	360 150	408 170
5.0	–	122 932	184 397	230 496	261 229

The cells show the required number of person-years to observe rates in five scenarios at given levels of precision.

This calculation is for the overall background or all-cause thrombocytopenia incidence rate. Thrombocytopenia following vaccination will be addressed in the analysis.

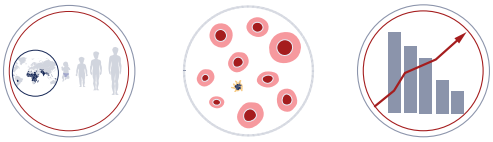
It is important to note that the cited incidence range is based on information from high-income settings. This may not be directly applicable to LMICs because such information from LMICs is limited.

5.8.2 Statistical analyses

The thrombocytopenia incidence rates will be calculated as the total number of confirmed cases divided by the total person-years of observation and expressed per 100 000 person-years. The estimation of person-years from the catchment population is described in Section 5.5. Incidence rates for thrombocytopenia following vaccination (secondary objective) will be similarly determined.

The analysis will be fully described in a written and approved statistical analysis plan. All analyses will be conducted using R statistical software *(29)*. Annual and, when feasible, monthly rates to assess the seasonality of outcomes will be calculated with their corresponding Poisson 95% confidence intervals.

All rates will be stratified by sex, age (5–23 months, 2–5 years, 6–11 years, 11–15 years; strata to be specified in the statistical analysis plan) corresponding to the ages targeted for dengue, malaria and other routine vaccines, site and country. The main incidence rate will be calculated using all cases regardless of vaccination status (primary objective). In addition, adjustments will be made in accordance to the 6 week vaccination history (secondary objective). The WHO Pharmacovigilance team will coordinate all the primary analyses. Any secondary outcomes or analyses will be decided by the study sites and the WHO Pharmacovigilance team.



5.9 Data management

The study will be implemented at the site level under the responsibility of the site principal investigator. A data management plan will be developed before initiation of the study. The data management plan will describe all the steps involved in data collection, cleaning and validation. Site-specific data management plans will be developed to allow for differences between study sites. The study sites will be responsible for collecting, cleaning and validating the data. The study sites will be responsible for managing the database with the support of the WHO Pharmacovigilance team. The data collected by the study sites will be shared with the WHO Pharmacovigilance team, which will then conduct the primary statistical analyses. The data collected at each site will be owned by the respective site.

5.9.1 Electronic data capture system

The study will use an electronic data capture system consisting of a module installed on a handheld tablet synchronized with the site database in real time or at the end of each day. Unique identifiers will be used to identify study participants. The system will have a web module for study progress monitoring. The software used in the handheld device will be developed using open-source technologies (PHP and MySQL). Comprehensive training on the use of the electronic data capture system, including electronic case report form completion guidelines, will be provided. User testing will be performed before deployment. At the end of the study, the electronic data capture system will be handed over to the study sites to promote the long-term sustainability of vaccine safety surveillance.

Mobile device module

The module will be used at sites for recruitment, data collection through electronic case report forms, tracking, on-site quality checks and validation. To ensure data integrity, skip patterns and logical checks will be configured into the electronic case report forms. The mobile module will support online and offline data entry. The data collected by the tablets will be uploaded in real time to the server or at the end of each day.

Web module

The web module will be used by the WHO Pharmacovigilance team to centrally monitor site activities such as tracking study progress and query management. The queries generated will be sent to the site for resolution.

Source documents

The only source documents that the study may require will be medical records. All information needed from health facility medical records will be identified before the start of the study. A request to the study site regarding access to medical records will be made in advance. Any scanned copies of source documents will be accessed only by authorized study personnel within the study site.

5.9.2 Data quality

Data quality will be assessed at all stages of the study, from the point of collection to analysis. Immediately after data collection, the information collected will be verified for completeness by the study data manager. The electronic case report forms will include configurable checks to immediately detect missing data, out-of-range values, illogical entries and other potential errors. Manual cleaning processes will be used to detect anomalous data. Concurrent manual data review will be conducted. Any queries that arise will be generated within the electronic data capture system and resolved.

5.9.3 Data security

The General Data Protection Regulation (GDPR) will apply *(30)*. The devices and modules (including web-based modules) will have secure login features to access data. The system will use a Secure Socket Layer (SSL) certificate with 256-bit SSL to secure data transfer. Study teams will be provided with login credentials with rights assigned for specific roles. Site principal investigators and other designated study staff will have access to a supervisory web module enabling them to view data pertaining to their respective sites and monitor the progress of the study in real time. Study sites will have access only to their study data and not data from other collaborating sites. Only authorized study staff and WHO Pharmacovigilance team members (e.g. software developers and database administrators) will have access to study data from all sites.

Data storage

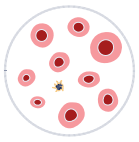
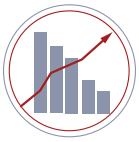
Data will be stored in a secure server complying with data safety regulations for patient personal health information.

File retention and archiving

GDPR will be applied to data storage and archiving. All original source documentation is expected to be stored at the site for five years, or according to the local applicable regulations. The sites will notify the WHO Pharmacovigilance team before any destruction of participant medical records.

5.10 Monitoring and quality assurance

A site initiation visit will be conducted to ensure the site is ready to start data collection. Study staff will be trained on the study procedures, and a training plan with routine refresher sessions will be maintained. Remote and, when possible, on-site monitoring of the study will be performed throughout the study to assess compliance with the protocol, adherence to the study procedures, and accuracy and completeness of the data.

6. Study management

6.1 Study implementation structure

6.1.1 Scientific advisory committee

A dedicated scientific committee (to be detailed in the site-specific protocol) will oversee the implementation and running of the study. The committee will provide scientific, statistical and technical expertise, as needed.

6.1.2 WHO Pharmacovigilance team

The WHO Pharmacovigilance team will be responsible for site selection, overall study coordination and management, development of study protocols, data collection tools and operating procedures, study monitoring and data quality assurance, data analysis and result dissemination.

6.1.3 National focal points

National focal points will comprise representatives from national and local immunization programmes, national and local health management teams, national and local maternal and child health programmes, drug regulatory authorities and research ethics committees. National focal points are responsible for facilitating site selection, training, ethics, administrative clearance for study initiation, participating in study monitoring and quality assurance.

6.1.4 Site team

The site team will comprise a site principal investigator and co-principal investigator, a paediatrician, a haematologist, and research staff, who may be dedicated study or health facility staff. The study team will be responsible for ethics and approval at the site level, obtaining informed consent, data collection and monitoring study progress.

6.1.5 Changes to the protocol

Any changes to the protocol will be documented as amendments. Amendments that impact the study objectives, procedures and participant safety will require submission to the WHO Research Ethics Review Committee and all relevant local independent ethics committees or institutional review boards for approval. Amendments will not be implemented until approval has been obtained. Minor amendments, such as a change of staff in the study site, will be intimated to the relevant independent ethics committee or institutional review board as appropriate. Any amendment that may have an impact on a participant's agreement to be part of the study will require re-consent.

6.2 Guiding principles

The study will be conducted according to the International Ethical Guidelines for Health-related Research Involving Humans *(30)*, under the principles of the Declaration of Helsinki *(15)*, and considering local legislation on medical research in humans and data sharing from clinical records beyond national or administrative borders.

This is an observational study that does not involve any medical interventions or modifications to clinical and diagnostic procedures. There are no direct benefits or risks to the participants. There are, however, significant potential societal advantages associated with this international study that intend to enhance safety monitoring of vaccination programmes. The long-term goal is to establish robust and sustainable public health surveillance systems in countries, with the capacity to consistently gather high-quality data to monitor vaccine safety.

6.3 Respecting participant autonomy

Participants will be informed during the consent process that their participation in the study is entirely voluntary, and they can withdraw consent at any time during the study.

Participating health facilities can choose to implement one or both of the following approaches to obtaining informed consent:

- Study-specific informed consent before case identification: based on the screening criteria, potential participants are approached for informed consent upon admission to the paediatric or adult ward, before knowing whether they are eligible for the study.
- Broad informed consent upon registration at the health facility, as per the health facility's standard operation procedures: this option is available only to health facilities that routinely ask people for informed consent to use their data for research purposes.

6.4 Maintaining participant confidentiality

Data confidentially will be maintained at all times according to global and local regulatory requirements. Paper records will be kept in locked cabinets in the health facility. Electronic data will be stored in secure databases with encryption and strict access control, de-identified for analysis, and reported in an aggregated or anonymized manner to prevent identification. Only authorized study team members will have access to data with individual identifiers. Access to the study data will be controlled and will be limited to the principal investigators, people selected to perform quality and consistency checks, and the study statistician. All research staff must be trained in these confidentiality measures. A clear plan for the secure handling and eventual destruction of data will be rigorously followed.

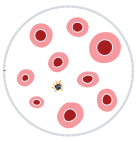
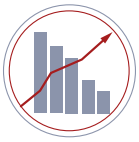
6.5 Data sharing

After the primary objectives of the study have been achieved and published, de-identified data will be shared upon reasonable request made to the study teams and the WHO Pharmacovigilance team. Data should be shared in accordance with WHO policy, and anonymized metadata should be available in a repository. Any further research using data from the study must be approved by the local or national regulatory authorities to ensure the interests of participants and their communities are protected. If further research deviates from the original research question or participants need to be contacted for information other than that specified in the consent form, a new consent/assent form will be issued. Extra care must be taken to protect the privacy and confidentiality of children.

6.6 Independent ethics committee or institutional review board

WHO will ensure the master protocol and any amendments, with specific details about the study sites, are submitted to the WHO Research Ethics Review Committee for review and approval. The Committee should have members with expertise in paediatric research, ethics and child health or be able to consult with such experts, because the study involves children.

Each participating site will be responsible for submission of the study protocol and any amendment to the respective local, national or independent ethics committees and/or institutional reviews boards, according to local requirements. Any additional regulatory clearances, as required by the country law and regulations, will be adhered to in respect of each participating site.

7. Dissemination of study results

7.1 Study report

A study report with all the findings will be made available by the study team to the national health authorities within an agreed period. The results will be communicated to the participating sites once the report is finalized.

7.2 Dissemination strategy

The dissemination actions will comprise at least the following:

- publication of scientific papers in an open-access format, consistent with good publication practices, with authorship and co-authorship agreed between the WHO Pharmacovigilance team and study sites;
- participation in scientific meetings with oral or poster presentations;
- a study report for the national health authorities with all the findings, made available by the study team within an agreed period.

7.3 Communicating findings to participants

Findings will be available after one year from the start of the study. A summary of the findings will be shared with participants via email, telephone or the study website, or by the clinical team during health facility follow-up visits.

8. Study limitations

A major limitation of the study design is the method used to estimate person-years at risk, which assumes the population is stable, with no major shocks in the population dynamics within the catchment area – that is, the number of births, deaths and migrations does not change significantly. If there are significant changes in the population (e.g. seasonal migration for employment), the estimate of person-years at risk may be inaccurate. This will vary depending on the site but will be considered in the site-specific protocols.

Accurate measurement of the incidence rate of thrombocytopenia following vaccination will be a challenge, because information on vaccination will be self-reported and such information can potentially be unreliable and result in recall bias. As a result, the rates of thrombocytopenia following vaccination may not be a true representation. This needs to be considered when interpreting results. Attempts to mitigate this include asking participants about vaccination cards and vaccination reminders, checking medical records, and prompting participants with particular questions – but the uncertainty still remains.

The sample size calculation used in the protocol is derived from estimates in high-income countries and may differ from the incidence of thrombocytopenia in LMICs.

The selected health facility may underreport cases of thrombocytopenia due to overlapping catchment areas between competing health facilities. A workaround for this is to conduct the study in all competing facilities that share a service area.

Not all participating health facilities may be able to access the required laboratory tests for accurate identification of thrombocytopenia (see Annex 1). This may contribute to between-site heterogeneity in people fulfilling the case definition for thrombocytopenia.

If the length of the study period is longer than, for example, one year, recurrent thrombocytopenia cases (defined as a person with previous admission with thrombocytopenia within one year) must be identified and excluded from the calculation of background rates.

People who do not consent to participate will be excluded from the study, which may impact the estimates of thrombocytopenia. Mild thrombocytopenia may not be captured because it does not have any clinical symptoms.

Selecting health facilities with good diagnostic tools is important for accurate diagnoses and data, meaning participants are drawn mostly from well-equipped health facilities. This could lead to bias, since these populations might differ from those in rural areas or less well-equipped health facilities. This bias will be addressed by describing the areas around the study sites and noting the limitations in applying the findings to a wider population.

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Annex 1. Health facility screening questionnaire

Version 1, 26 March 2025: This questionnaire collects information on potential study site characteristics, how patient data are recorded, and resources available. The purpose of the data collected is to support the decision to select the health facility as a study site and to understand the baseline characteristics for interpretation of the findings. The form should be filled by potential site principal investigators expressing an interest in the study. The information can be obtained from health facility administration records. The questionnaire takes 10–20 minutes to fill.

	Part 1. General information		**Comments**
1	Health facility name and address		
2	Name and function of respondent		
3	Email address of respondent		
4	Country		
5	Full address		
6	Number of beds in health facility		
7	Number of paediatric (aged <15 years) admissions per year		
8	Type of health facility	Primary ☐ Secondary ☐ Tertiary ☐	
9	Which of the following types of care are provided?	Antenatal ☐ Maternity ☐ Paediatric ☐ Other ☐ *If other, specify:*	
10	Is the health facility public or private?	Public ☐ Private ☐	
11	Is the population served primarily urban or rural?	Primarily urban ☐ Primarily rural ☐ Mixed ☐	
12	Estimated catchment population		

Part 2. Patient data recording			Comments
13	How are patient data recorded? *Check all that apply*	Electronically and stored in a database ☐ Paper-based and stored in a physical archive ☐	
14	Is internet access available to allow for data entry?	Yes ☐ No ☐	
15	If there is a database or archive with patient data available (e.g. patient charts or discharge registry), can it be used for research purposes?	Yes ☐ No ☐	
16	Does your site distinguish primary diagnoses from other diagnoses?	Yes ☐ No ☐	
17	Are discharge diagnoses recorded in a database or registry?	Yes ☐ No ☐	
18	Are outpatient diagnoses captured in a database or registry?	Yes ☐ No ☐	
19a	Is a unique identifier used for each patient?	Yes ☐ No ☐	
19b	If unique identifiers are used, is the same identifier used across departments (e.g. antenatal, maternity, neonatal and paediatric wards)?	Yes ☐ No ☐	
19c	If unique identifiers are used, is the same identifier used for outpatient care?	Yes ☐ No ☐	
19d	If unique identifiers are used, is the same identifier used for laboratory data?	Yes ☐ No ☐	
20	Are individual patient charts easily accessible in the database or archive?	Yes ☐ No ☐	
21a	Is a trained physician or nurse available to participate in the study to review medical records against case definition criteria and complete case report forms?	Yes ☐ No ☐	
21b	If a trained physician or nurse is available to participate in the study, do they have experience in research, including in data collection for research project?	Yes ☐ No ☐	
Part 3. Thrombocytopenia			
22	Does the health facility have a resident haematologist?	Yes ☐ No ☐	

Part 4. Laboratory			Comments
23a	Is there a laboratory available to the health facility?	Yes ☐ No ☐	
23b	If there is a laboratory available to the health facility, could blood tests (e.g. platelet count, oxygenation, peripheral blood smear) be done?	Yes ☐ No ☐	
23c	Are laboratory results recorded in health facility records or a database?	Yes ☐ No ☐ Both ☐	
23d	If no laboratory is available, does an outsourcing system exist?	Yes ☐ No ☐	

Annex 2. Informed assent form

Hi there! This form is for kids aged 8–12 years. You are here to see the doctor or nurse to get some care.

My name is [name of staff member].

I want to talk to you about something called thrombocytopenia. Let's call it TP. This is a special word for when your body doesn't have enough little helpers called platelets. Platelets are like tiny repair workers in your blood that help stop bleeding when you get a cut. Only a very few people get TP. It's like finding a special rare stone.

We are doing a special learning project, like being detectives, to learn more about TP. We just want to watch and learn from information your doctor and nurse already have about you. We won't give you any new medicine or change how the doctor takes care of you at all.

Sometimes people wonder if getting a shot – a vaccine – can make someone get TP. This learning project can help us understand how often TP happens to kids in general, so doctors can learn more about it. This helps keep kids healthy.

We are doing this learning project at [number of sites] hospitals or clinics in [number of countries] countries. Your hospital or clinic is one of them. We will be learning from the information for [number of years] years.

We will only use information that your doctor or nurse already wrote down when you came here for care. We won't ask you extra questions or do extra tests just for this project. Nothing will change about how the doctors and nurses take care of you because you are in this project.

You won't get better just from being in this learning project. But the information from lots of kids in all the hospitals will go into a safe place, like a secret box, so smart people can study it. This helps them learn more about TP and how to help kids in the future. It can also help hospitals and clinics do an even better job of taking care of people.

Don't worry – your name, address or anything that tells people who you are will not be on the information we use. It will be like a secret code number instead. Nobody will know it's you. Your information will be kept very safe.

The information from your hospital will be sent to a safe computer place in [where data will be stored]. Smart people will look at the information to learn more. They promise to keep it a secret and follow rules to keep your information safe.

Grown-ups called [names of study sponsors] are helping us do this learning project.

It's totally your choice whether the information from your doctor or nurse can be used for this learning project. It's like being a helper for other kids.

If it's OK with you, and your mum or dad or the grown-up who takes care of you says it's OK too, you will both sign your names on a piece of paper.

If you change your mind later, that's OK. You can tell [name of staff member talking to them or study principal investigator] or your mum or dad, and they will tell us not to use your information any more.

You can also say no right now. It is totally OK to say no. If you say no, the doctors and nurses will still take just as good care of you at the hospital. Nothing about your care will change.

Do you have any questions for me?

Minor aged 8 to <12 years:

I agree to take part in the research ..... (initialled by child)

Or

I do not wish to take part in the research, and I have signed the assent below: ..... (initialled by child)

Print name of child: .....

Signature of child: .....

Date (day/month/year): ...../...../.....

Parent or legally authorized representative

I am the parent or legally authorized representative of the potential participant. I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions and all questions have been answered to my satisfaction. I hereby give consent on behalf of my

.....

Print name of parent or legally authorized representative: .....

Signature of parent or legally authorized representative: .....

Thumbprint of parent or legally authorized representative if applicable: .....

Date (day/month/year): ...../...../.....

Statement by the researcher or person taking consent

I have accurately read out the information sheet to the potential participant. I confirm that the child and their parent or legally authorized representative were given every opportunity to ask questions about the study, and all the questions asked to have been answered correctly and to the best of my ability. I confirm that the consent has been given freely and voluntarily, and that the child and their parent or legally authorized representative have not been coerced into giving consent. A copy of this informed consent form has been provided to the participant.

Print name of researcher or person taking the consent: .....

Signature of researcher or person taking the consent: .....

Date (day/month/year): ...../...../.....

Annex 3. Informed assent form

This informed consent form is for children and adolescents aged 12 to <15 years. You are visiting this health facility to receive care.

My name is [name of staff] and my job is to research occurrence of a condition called thrombocytopenia or TP.

I am going to give you information and invite you to be part of an observational research study (a study that observes people without an intervention or changing their care) to understand the rate of occurrence of TP. TP is a rarely occurring medical condition that leads to a low blood platelet count. Platelets help blood clot. Rarely, some cases of TP are thought to occur following vaccination. Studies such as this one are essential for ensuring the continued safety of vaccines. By understanding the rate of occurrence of TP in the general community, researchers can determine whether there is any increase in cases of TP when new vaccination programmes are introduced.

This research is going to be conducted in [number of sites] health facilities in [number of countries] countries. The health facilities will be collecting information for [number of years] years. In this research, information about your admission collected in the health facility as part of routine care may be used. There will be no change in the health facility practice. There will be no direct benefit to you due to this research, and the risks are minimal.

Information gathered from several people from the multiple health facilities that take part in this study will be transferred in a safe and confidential way to a database that will be studied by the World Health Organization (WHO). This will then support future research and detection and reporting of health problems or side-effects (known as adverse events of special interest, or AESIs) before and after new vaccines are introduced. This will also help in planning steps to improve the health facility data collection and recording practices, which will benefit people in the future.

All information used for research will not bear the name, address or any other personal information about you that will trace your identity. So, your individual identity will be protected. The health facility will assign a responsible person to use and store the research data in a safe place.

Your key-coded data obtained from this study will be stored in a secured database located in [where data will be stored]. The study data will be sent to WHO and any partners working with WHO for review or scientific analysis. It may also be added to research databases and used in the future by WHO and other organizations and people working for or with WHO to improve future research and to improve the detection and reporting of AESIs. Your personal data will always be handled in accordance with all applicable data protection and privacy laws and will be communicated only to authorized people, including WHO and their representatives and agents. Any information collected from other physicians will be handled in the same confidential manner as that collected by the study doctor.

The study sponsor is [name of study sponsor], and the principal investigators are [to be completed by country teams].

If you are willing to allow the information collected in the health facility as part of routine care about you be used for this research, you and your parent or legally authorized representative will sign and date this form. You are free to contact [study principal investigator] to understand how your information has been made use of. If at any time you do not wish to share your information, you are free to contact [study principal investigator] and withdraw from this study.

You also have the choice to say no and opt out of this research. By doing so, rest assured your care in the health facility will not be affected in any way.

Minor aged 12 to <15 years:

I agree to take part in the research .....(initialled by child or adolescent)

Or

I do not wish to take part in the research, and I have signed the assent below

.....(initialled by child or adolescent)

Print name of child or adolescent: .....

Signature of child or adolescent: .....

Date (day/month/year): ...../...../.....

Parent or legally authorized representative

I am the parent or legally authorized representative of the potential participant. I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions, and all questions have been answered to my satisfaction. I hereby give consent on behalf of my

.....

Print name of parent or legally authorized representative:.....

Signature of parent or legally authorized representative: .....

Thumbprint of parent or legally authorized representative if applicable: .....

Date (day/month/year): ...../...../.....

Statement by the researcher or person taking consent

I have accurately read out the information sheet to the potential participant. I confirm that the child and their parent or legally authorized representative were given every opportunity to ask questions about the study, and all the questions asked to have been answered correctly and to the best of my ability. I confirm that the consent has been given freely and voluntarily, and that the child and their parent or legally authorized representative have not been coerced into giving consent. A copy of this informed consent form has been provided to the participant and their parent or legally authorized representative.

Print name of researcher or person taking the consent: .....

Signature of researcher or person taking the consent: .....

Date (day/month/year): ...../...../.....

Annex 4. Informed consent form for parents

This informed consent form is for parents or legally authorized representatives of children participating in an observational research study on the occurrence of thrombocytopenia. Your child is visiting this health facility to receive care.

Introduction

My name is [name of staff]. I am conducting research on the occurrence of a condition called thrombocytopenia (TP). TP is a medical condition that leads to a low blood platelet count. Platelets help blood clot. Rarely, some cases of TP are thought to occur following vaccination. This study aims to understand the rate of occurrence of TP in the general community to ensure the continued safety of vaccines.

Purpose of the study

This research will be conducted in [number of sites] health facilities across [number of countries] countries over [number of years] years. Information about your child's admission, collected as part of routine care, may be used for this research. There will be no change in health facility practices, no direct benefit and minimal risk to your child from this research. The information gathered will support future research and improve the detection and reporting of adverse events of special interest (AESIs) before and after new vaccines are introduced. There is a possibility that the findings will be used for other research in the future.

Confidentiality

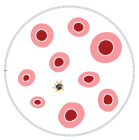
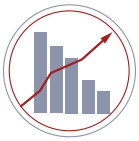
All information used for research will be anonymized to protect your child's identity. The health facility will assign a responsible person to store the research data securely. Your child's key-coded data will be stored in a secured database located in [where data will be stored]. The study data will be sent to the World Health Organization (WHO) and any partners working with WHO for review or scientific analysis. There is a possibility that findings will be used for other research in the future. Your child's personal data will always be handled with strict confidentiality in accordance with applicable data protection and privacy laws.

Voluntary participation

Participation in this study is entirely voluntary. You may choose to withdraw your child from the study at any time without affecting their care at the health facility. If you agree to your child's participation, you will sign and date this form. You are free to contact [STUDY PRINCIPAL INVESTIGATOR] to understand how your child's information is being used.

Contact information

For further information or to withdraw your child from the study, please contact [study principal investigator].

Consent

I have read the information provided, or it has been read to me. I have had the opportunity to ask questions, and all my questions have been answered to my satisfaction. I voluntarily agree to my child's participation in this study.

Print name of parent or legally authorized representative: .....

Signature of parent or legally authorized representative: .....

Date (day/month/year): ...../...../.....

Statement by the researcher or person taking consent

I have accurately read out the information sheet to the parent or legally authorized representative. I confirm that the parent or legally authorized representative was given every opportunity to ask questions about the study, and all questions asked have been answered correctly and to the best of my ability. I confirm that the consent has been given freely and voluntarily, and that the parent or legally authorized representative has not been coerced into giving consent. A copy of this informed consent form has been provided to the parent or legally authorized representative.

Print name of researcher or person taking the consent: .....

Signature of researcher or person taking the consent: .....

Date (day/month/year): ...../...../.....

Annex 5. Brighton Collaboration case definition of thrombocytopenia

The Brighton Collaboration has developed a case definition for thrombocytopenia to standardize the identification and classification of this condition, particularly in the context of vaccine safety monitoring. It includes specific clinical and laboratory criteria, different levels of diagnostic certainty, and guidelines for data collection and analyses. This approach ensures consistency across studies and improves understanding of thrombocytopenia as an adverse event following immunization. The case report form in Annex 6 should be used to collect information needed to diagnose thrombocytopenia. The diagnosis and level of certainty should be carried out by a trained specialist. The time taken to make a diagnosis of thrombocytopenia depends on the amount of data available and experience of using the definitions.

- Level 1 of diagnostic certainty (confirmed thrombocytopenia):
  - platelet count below 150 × 109 L−1;

  and

  - confirmed by a blood smear examination **or** clinical signs and symptoms of spontaneous bleeding.
- Level 2 of diagnostic certainty (unconfirmed thrombocytopenia):
  - platelet count below $150 \times 10^9 L^{-1}$.
- Level 3 of diagnostic certainty:
  - not applicable

Annex 6. Thrombocytopenia case report form

Version 1, 26 March 2025: This case report form is designed to collect baseline information for suspected cases of thrombocytopenia. The questionnaire should be administered by trained and authorized study staff and data mangers. Information sources include face-to-face, telephone, virtual or electronic interview with potential participants and medical notes. The questionnaire will take less than 15 minutes to complete. Medical notes should be accessed only by people authorized to do so.

Part 1		
	Characteristics of potential participant	If interviewing a representative of the potential participant, check this box ☐ **Relationship to the potential participant:** .....
1a	Age of potential participant in completed years at time of presentation to health facility	.....
1b	Sex of participant at birth	Male ☐ Female ☐
1c	Place of residence	.....
	Give closest town centre	.....
Part 2. Clinical signs and symptoms and investigation results		
2a	Initial or admission diagnosis	.....
2b	Date of initial diagnosis	dd/mm/yyyy ...../...../.....
2c	Date of symptom onset	dd/mm/yyyy ...../...../.....
2d	Was a physical examination performed?	Yes ☐ No ☐ Unknown ☐ *If no or unknown, skip to Question 4a*
2e	What was the date of the physical examination?	dd/mm/yyyy ...../...../.....
2f	Which of the following clinical signs were present at presentation at the health facility?	Bruising ☐ Purpura ☐ Haemorrhagic oozing of skin lesion ☐ Conjunctival bleeding ☐ Vaginal bleeding (unless mensurating) ☐ Epistaxis ☐ Petechiae ☐ Haematuria ☐ Haematoma ☐ Haematemesis ☐ Haematochezia ☐ Occult bleeding from rectum ☐

Part 1 *(continued)*

2g Was there a medical confirmation of the symptoms?

- Yes ☐
- No ☐
- Unknown ☐

2h By whom was the medical confirmation given?

- General practice physician ☐
- Specialist ☐

If specialist, specify: .....

- Clinical officer ☐
- Other ☐

If other, specify: .....

Part 3. Platelet count

3a Was a complete blood count performed?

- Yes ☐
- No ☐
- Unknown ☐

If no or unknown, go to Question 6a

3b When was the complete blood count done?

dd/mm/yyyy ...../...../.....

3c How was the platelet count done?

- Automated haematology analyser ☐
- Cell count slide ☐

3d What was the platelet count?

..... × 10^9/litre

3e Was there a medical confirmation of the complete blood count?

- Yes ☐
- No ☐
- Unknown ☐

3f By whom was the medical confirmation given?

- General practice physician ☐
- Specialist ☐
- Clinical officer ☐

Part 4. Peripheral blood smear examination

4a Was a peripheral blood smear examination performed?

- Yes ☐
- No ☐
- Unknown ☐

If no or unknown, go to Question 6a

4b When was the blood smear examination done?

dd/mm/yyyy ...../...../.....

4c What were the results of the blood smear examination?

- Reduced platelet numbers with no clumping seen ☐
- Normal platelet numbers or clumping seen ☐
- Unknown ☐

Part 4. Peripheral blood smear examination *(continued)*

4d Was there a medical confirmation of the blood smear results?

- Yes ☐
- No ☐
- Unknown ☐

4e By whom was the medical confirmation given?

- General practice physician ☐
- Specialist ☐

If specialist, specify: .....

- Clinical officer ☐

Part 5. Clinical history

5a In the past six weeks, has the potential participant experienced diarrhoeal or respiratory illness (including influenza-like illness and only mild symptoms), with or without fever?

- Diarrhoea ☐
- Respiratory illness ☐
- Other ☐

If other, specify: .....

- Potential participant has not been unwell ☐

5b What was the symptom onset date of the most recent episode of diarrhoea and/or respiratory illness (as applicable)?

Diarrhoea: dd/mm/yyyy ...../...../.....

Respiratory illness: dd/mm/yyyy ...../...../.....

5c Did the potential participant receive treatment in a health facility?

- Yes – in this health facility ☐
- Yes – in another health facility ☐
- No – did not receive treatment ☐
- Unknown ☐

5d If the potential participant experienced diarrhoeal or respiratory illness (with or without fever), were any laboratory tests performed to confirm the underlying pathogen?

- Test performed to confirm diarrhoeal illness ☐
- Test performed to confirm respiratory illness ☐
- Test not performed ☐
- Unknown ☐

5e If yes to Question 5d, what were the results of the test?

.....

5f Does the potential participant have a history of thrombocytopenia from other causes (e.g. due to dengue, malaria, nutritional deficiencies, leukaemia, aplastic anaemia)

- No history of thrombocytopenia ☐
- Yes – history of:
  - Dengue ☐
  - Malaria ☐
  - Nutritional deficiencies ☐
  - Leukaemia ☐
  - Aplastic anaemia ☐
  - Other ☐

If other, specify: .....

- Unknown ☐

Part 6. Immunization history

6a Did the potential participant receive any vaccine(s) in the past six weeks?

Please answer "yes" or "no" only if there is documented evidence; otherwise answer "unknown"

Yes ☐
No ☐
Unknown ☐

If no or unknown, end of questionnaire

6b If yes to Question 6a, which vaccines (vaccine types [antigen] and dose number) were administered, with dates of vaccine administration?

Enter more than one item if the participant was vaccinated with more than one vaccine type and/or more than one dose

Vaccine 1:

Type: .....

Dose number: .....

Date: (dd/mm/yyyy): ...../...../.....

Date unknown ☐

Vaccine 2:

Type: .....

Dose number: .....

Date: (dd/mm/yyyy): ...../...../.....

Date unknown ☐

Vaccine 3:

Type: .....

Dose number: .....

Date: (dd/mm/yyyy): ...../...../.....

Date unknown ☐

Vaccine 4:

Type: .....

Dose number: .....

Date: (dd/mm/yyyy): ...../...../.....

Date unknown ☐

Annex 7. Expected timelines and adaption of protocol

Month/year	Task
...../.....	Preparation of electronic data capture system
...../.....	Development of site-specific study procedures
...../.....	Obtaining approval of WHO Research Ethics Review Committee and local approvals
...../.....	Preparation of administrative approvals
...../.....	Workshops (training on protocol and electronic data capture system)
...../.....	Case dentification
...../.....	Data collection, data monitoring, data cleaning
...../.....	Data analysis
...../.....	Study report

Documentation of protocol amendments

Version	Date	Reason for new version

Annex 8. Study team and responsibilities

Scientific advisory committee

Name	Title (organization)	Email

WHO Pharmacovigilance team

Name	Organization	Role	Email

National focal points

Name	Title (organization)	Email

For more information, please contact:

Regulation and Prequalification Department (RPQ)
Regulation and Safety (REG)
Pharmacovigilance (PVG)
World Health Organization
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CH-1211 Geneva 27
Switzerland

Email: pvsupport@who.int