Annex
to Regulations of central and regional group of quick response to AEFI/tuberculin diagnostics (subitem 1 of item 12)

PROTOCOL
of investigation and establishment of a causal association between serious and/or cluster of AEFI/tuberculin diagnostics and use of vaccine, tuberculin

Investigation and establishment of a causal association between serious and/or cluster of AEFI/tuberculin diagnostics and use of vaccine, tuberculin consists of 4 steps.

Step 1. Collection of information related to development of serious and/or cluster of AEFI after use of vaccine, tuberculin

I. General information

Name of enterprise, institution, organization where immunization/tuberculin diagnostics took place_____
_____

Category of immunization or tuberculin diagnostics:
□ mass campaign
□ vaccination by age
□ preschool
□ school
□ immunization of travelers
□ tuberculin diagnostics
□ other (indicate)_____
_____
_____
_____

Place of immunization/tuberculin diagnostics
_____
_____

Full name of person submitting protocol
_____
_____
Position _____
_____
_____

Date of investigation ___ /___/_____
Date of filing protocol __ /___/_____
This protocol is
□ primary
□ interim
□ final

Place of work_____
Office phone (with code)_____
Mobile _____
E-mail_____

Information about person, in whom vaccine/tuberculin was used:
Full name_____
Sex □ M □ F
Date of birth (dd/mm/yyyy) ___ /___/_____
Address of person, in whom vaccine/tuberculin was used (city/village/settlement, street name, house number, phone number, etc.)
_____
_____
_____
(for each case of cluster of AEFI an individual protocol form shall be filled in)

Trade name of vaccine(s)/ diluent or tuberculin, previously received	Date of vaccination/ tuberculin diagnostics	Time of vaccination/ tuberculin diagnostics	Dose (first, second, etc.)	Batch number	Expiration date
				Vaccine or tuberculin	Vaccine or tuberculin
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent

Site of vaccine/tuberculin injection
□ left shoulder
□ right shoulder
□ shoulder (not specified)
□ left hip
□ right hip
□ hip (not specified)
□ left forearm
□ right forearm
□ forearm (not specified)
Date of first/key symptom of AEFI (dd/mm/yyyy) ___ /___/_____
Time of first symptom of AEFI (hours/min) ___ /___
Date of hospitalization (dd/mm/yyyy) ___ /___/_____
Date of first visit to a health facility because of AEFI (dd/mm/yyyy) ___/___/___
Status on date of investigation of AEFI:
□ death
□ invalidity
□ recovering
□ recovery without sequela

□ recovery with sequela
□ without changes
□ unknown
If died, date and time of death shall be indicated (dd/mm/yyyy) _ /__/_ (hh/mm) _ /_
Autopsy done
□ yes (date) (dd/mm/yyyy) ___ /___/_____
□ no
□ planned on (date) (dd/mm/yyyy) ___ /___/_____ time (hh/mm) ___ /___
Comments on results of autopsy shall be attached
(if any)_____ _____
_____
_____
_____
_____
_____

II. Available information about person in whom vaccine/tuberculin were used prior to vaccination/tuberculin diagnostics

Criteria	Result	In case of positive response a comment shall be provided
Past history of similar AEFI regardless of vaccination/tuberculin diagnostics	Yes/No/Unknown	
Similar AEFI after previous vaccination/tuberculin diagnostics	Yes/No/Unknown	
Burdened history of allergy to vaccine/tuberculin, medicinal product or food, etc.	Yes/No/Unknown	
Burdened family history of allergy (availability of diseases which caused AEFI)	Yes/No/Unknown	
History of hospitalization in last 30 days with cause	Yes/No/Unknown	
Person in whom vaccine/tuberculin was used currently on concomitant medication	Yes/No/Unknown	
If yes, indicate trade name of medicinal product, indication, dose and date of start and end of treatment		
Whether any disease preceded the development of AEFI (30 days)/availability of genetic disorders	Yes/No/Unknown	

For adult women in whom vaccine was used it is necessary to indicate:
Currently pregnant
Yes (weeks)_____/No/Unknown
Currently breastfeeding

Yes/No/Unknown

For infants under 1year in whom vaccine was used, indicate:
Delivery procedure was:
□ full term □ preterm □ in term after 42 weeks of gestation
□ physiological □ caesarean section □ with complications (specify)
_____
_____
Birth weight _____ g
Newborn state according to Apgar scale _____

III. Details related to case of serious and/or cluster of AEFI after use of vaccine, tuberculin

Source of information (that applied)
□ medical examination
□ autopsy results
□ documents (indicate)
_____
Full name of person, who first examined/treated the person in whom immunization/tuberculin diagnostics were conducted
_____
Full name of other person, who consulted and gave medical care to person in whom immunization/tuberculin diagnostics were conducted
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
Other sources of information
_____
_____
_____
_____
_____
_____
Signs of AEFI in chronological order from the time of immunization/tuberculin diagnostics
_____
_____
_____
_____
_____

_____
_____

Full name of person who gave details about AEFI
_____
Position
_____
Place of work
_____
Office telephone (with code)
_____
Mobile
_____
E-mail
_____

Date (dd/mm/yyyy)
___ /___/_____
Time (hours/min)
___/___

Documents containing documented confirmation of patient's status (tick the necessary):
□ case sheet
□ discharge summary
□ consultation of main specialists
□ laboratory reports
□ results of instrumental studies
□ autopsy report:
    □ histological investigation
    □ virological investigation
    □ bacteriological investigation
    □ toxicological investigation

Provisional/final diagnosis _____
_____
_____
_____

IV. Details of vaccine/tuberculin in case of serious and/or cluster of AEFI

Number of persons in whom immunization and/or tuberculin diagnostics was conducted at enterprise, in institution, organization, oblast/city/district.
Attach record, if available
_____
_____
_____
_____

Trade name of vaccine/tuberculin
Number of doses/ tuberculin tests

1. Vaccine/tuberculin dose number in person, in whom were registered serious and/or cluster of AEFI

□ first □ second □ third □ forth □ fifth □ > five □ unknown

When vaccine is used from multidose vials, indicate the patient in series in whom vaccination was made □

If tuberculin is used indicate the patient in series in whom tuberculin diagnostics was made □

2. Was there an error in using vaccine, tuberculin because of non-adherence to information for their use (e.g. immunization and/or tuberculin diagnostics after vaccine, tuberculin expired, non-adherence to contraindications, etc.)	Yes*/No
3. Whether vaccine/tuberculin administered could have been unsterile	Yes*/No/Unable to assess
4. Whether physical condition of vaccine, tuberculin (colour, turbidity, foreign substances, etc.) was abnormal at the time of their administration	Yes*/No/Unable to assess
5.Whether an error was made by person conducting immunization/tuberculin diagnostics in: 1) dilution/preparation of vaccine (wrong medicinal product or wrong diluent was used, improper mixing, improper syringe filling, etc.); 2) use of tuberculin (wrong medicinal product used, improper syringe filling etc.)	Yes*/No/Unable to assess
6. Was the vaccine, tuberculin administered/used incorrectly (wrong dose or route of administration, wrong site of administration, wrong needle size etc.)	Yes*/No/Unable to assess

7. Number immunized from the concerned vial/ampoule with vaccine or number tested with the tuberculin diagnostics from the concerned vial/ampoule at particular enterprise, institution, organization where immunization/tuberculin diagnostics conducted

8. Number immunized with the concerned vaccine or number tested with concerned tuberculin while tuberculin diagnostics at particular enterprise, institution, organization on the same day

9. Number immunized with the concerned vaccine batch and number tested with concerned tuberculin batch while tuberculin diagnostics at particular enterprise, institution, organization on the same day.

10. Is this case a part of a cluster? Yes/No

If yes, indicate how many other cases have been detected in the cluster?

11. Did all the cases in the cluster receive vaccine/tuberculin diagnostics from the same vial/ampoule of vaccine/tuberculin	Yes/No

If no, indicate batch and number of vials/ampoules used in the cluster at conducting immunization/tuberculin diagnostics

* Enter details.

V. Information about enterprise, institution, organization where immunization/tuberculin diagnostics conducted

Syringes and needles used

Are AD syringes used for immunization/tuberculin diagnostics (to avoid repeated use)

If no, specify the type of syringes used:

□ Disposable

□ Other

_____

Specific key findings/additional observations and comments shall be indicated

_____

_____

_____

_____

Reconstitution: (complete only if diluent is applicable)

Reconstitution procedure

Same syringe used for vials of same vaccine	Yes/No/NA
Same syringe used for reconstituting different vaccines	Yes/No/NA
Separate reconstitution syringe for each vaccine vial	Yes/No/NA
Separate reconstitution syringe for each vaccination	Yes/No/NA
Are the vaccines and diluents used the same as those recommended by the manufacturer	Yes/No/NA

Specific key findings/additional observations and comments

_____

_____

_____

VI. Cold chain at storage and transport of vaccine/tuberculin

Vaccine/tuberculin storage in vaccination room

Is the temperature of the	Yes/No

vaccine/tuberculin storage refrigerator monitored

If "yes", was there any deviation outside of 2-8° C after the vaccine/tuberculin was placed in refrigerator — Yes/No

If "yes", provide details of temperature monitoring

_____

_____

Was the separate refrigerator for storing vaccines/tuberculin, diluents, syringes, needles used — Yes / No / Unkn

Was any other item other than vaccines/tuberculin, diluents, syringes, needles in the refrigerator (or freezer) — Yes / No / Unkn

Were any partially used reconstituted vaccines in the refrigerator — Yes / No / Unkn

Were any vaccines/tuberculin (expired, no label, frozen, with VVM of changed colour, etc.) in the refrigerator — Yes / No / Unkn

Were any diluents (expired, manufacturer/applicant not matched, microcracked, dirty vials/ampoules) in the refrigerator — Yes / No / Unkn

Specific key findings/additional observations and comments

_____

_____

_____

Type of carrier used to transport vaccine/tuberculin to vaccination room

Was the vaccine/tuberculin carrier sent on the same day as vaccination/ tuberculin diagnostics — Yes / No / Unkn

Was a conditioned ice-pack used — Yes / No / Unkn

Specific key findings/additional observations and comments

_____

_____

_____

_____

_____

_____

_____

VII. Community investigation

Were any similar clinical manifestations — Yes / No / Unkn

reported within a time period similar to
when AEFI occurred in the same locality
If yes, indicate the background morbidity level by oblast/city, where AEFI was registered _____
_____
_____
_____

How many cases of AEFI of:
Vaccinated _____
Not vaccinated _____
Unknown _____
Other comments _____
_____
_____
_____

VIII. Other findings/observations/comments

_____
_____
_____

Step 2. Collection of information for establishing causal association between serious and/or cluster of AEFI and use of vaccine, tuberculin

I. Is there strong evidence for other causes

Does clinical examination, or laboratory tests on the patient, in whom vaccine, tuberculin were used, confirm another cause of serious and/or cluster of AEFI	Yes*/No/Unknown/NA	Remarks

II. Is there a known causal association between the development of AEFI and use of the vaccine/tuberculin or vaccination/tuberculin diagnostics

Vaccine, tuberculin-related reaction (underline the appropriate)

1. Is there evidence in the medical and scientific literature that this vaccine/ tuberculin may cause the reported AEFI even if administered according to instruction for medical use	Yes*/No/Unknown/NA	Remarks
2. Did a specific laboratory test(s) demonstrate the causal	Yes*/No/Unknown/NA	Remarks

association between this AEFI and vaccine/tuberculin used		
Immunization/ tuberculin diagnostics program error-related reaction		
3. Was an error made by person conducting immunization/ tuberculin diagnostics at administration of vaccine/tuberculin because of non-adherence to recommendations for their use (e.g. immunization and/or tuberculin diagnostics beyond the expiry date of vaccine/tuberculin, non-adherence to contraindications etc.) (indicate whether vaccine, tuberculin were used in accordance with instruction for medical use in part of indications, contraindications, doses, regimen, storage conditions, etc. Vaccines from different manufacturers but of one type may have different specifications for medical use and failure to comply with them can result in AEFI)	Yes*/No/Unknown/NA	Remarks
4. Was the vaccine/tuberculin administered unsterile (indicate information related to availability or lack of signs specific to toxic shock syndrome (vomiting, diarrhoea, cyanosis and high temperature), and terms of their development (within a few hours), as well as local tenderness and tissue infiltration)	Yes*/No/Unknown/NA	Remarks
5. Was the vaccine's/ tuberculin physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal at the time of administration (indicate information related to availability or lack of abnormal colour (turbidity or presence of foreign substances, which may confirm that the vaccine contents are abnormal and may have caused the AEFI)	Yes*/No/Unknown/NA	Remarks

6. Was an error made by person conducting immunization/ tuberculin diagnostics in: 1) vaccine constitution/preparation (e.g. wrong medicinal product, wrong diluent, improper mixing, improper syringe filling, wrong dose, etc.); 2) tuberculin use (e.g. wrong medicinal product, improper syringe filling, wrong dose, etc.);	Yes*/No/Unknown/NA	Remarks
7. Was an error made by person in charge at transport, storage of vaccine/tuberculin (a break in the cold chain)	Yes*/No/Unknown/NA	Remarks
8. Was an error made by person conducting immunization/ tuberculin diagnostics at administration/use of vaccine/tuberculin (wrong dose or route of administration, wrong site of administration; wrong needle size etc.) (indicate whether the age-specific dose, site and route of administration comply with instruction for medical use of specific vaccine)	Yes*/No/Unknown/NA	Remarks

Immunization/tuberculin diagnostics anxiety-related reaction

9. Could the AEFI have been caused by anxiety about the immunization/tuberculin diagnostics (vasovagal, hyperventilation or stress-related disorder, etc.) (indicate the child's age (adolescent specific event), place of immunization (preschool institution, school))	Yes*/No/Unknown/NA	Remarks

III. AEFI time window taking in account type of vaccine/tuberculin used

Did the AEFI occur within an appropriate time window after this vaccine/ tuberculin administration	Yes*/No/Unknown/NA	Remarks

IV. Strong evidence against a causal association

Is there strong evidence against a causal association	Yes*/No/Unknown/NA	Remarks
If yes, provide a justification		

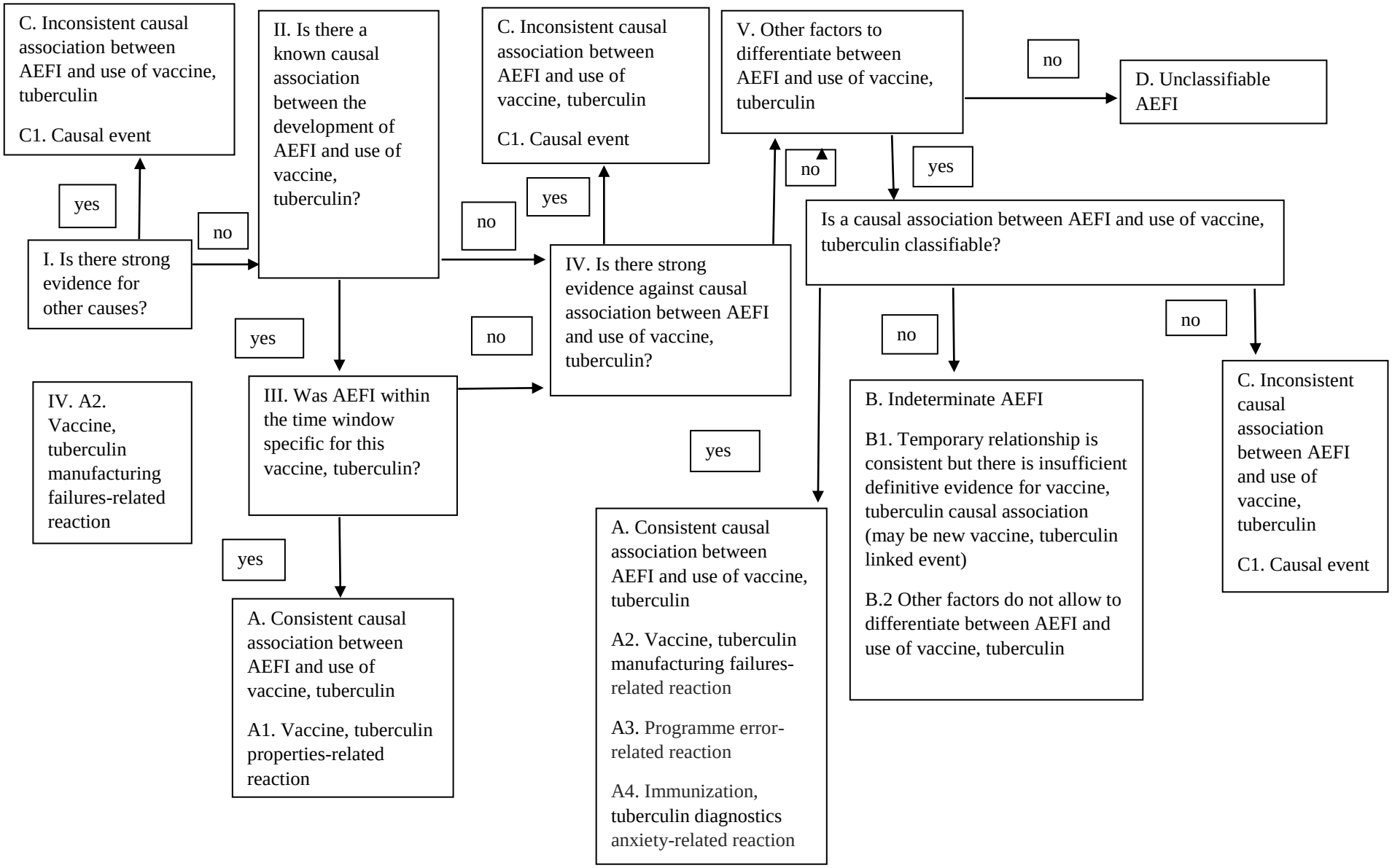
V. Other factors for differentiation between the development of AEFI and use of vaccine/tuberculin

1. Could the AEFI occur independently of vaccination/tuberculin diagnostics (background rate of morbidity in Autonomous Republic of Crimea/oblast/Kyiv, Sevastopol, where AEFI has been registered) (indicate the background rate of somatic and infectious diseases for different age-groups of population of administrative territorial unit which gives the ability to compare incidence of development of AEFI among vaccinated and non-vaccinated of one age-group who live in one administrative territorial unit)	Yes*/No/Unknown/NA	Remarks
2. Could the AEFI be a manifestation of another health condition	Yes*/No/Unknown/NA	Remarks
3. Did a comparable AEFI occur after a previous dose of a similar vaccine/tuberculin (indicate the history of previous vaccination to be analyzed in detail)	Yes*/No/Unknown/NA	Remarks
4. Was there exposure to a potential risk factor or toxin prior to the AEFI (indicate whether a surgical procedure or chemotherapy were conducted or medicinal products used prior to vaccination)	Yes*/No/Unknown/NA	Remarks
5. Was there acute illness prior to the AEFI	Yes*/No/Unknown/NA	Remarks

(indicate whether any disease occur prior to vaccination, AEFI may be the cause of this disease in post-vaccination period)		
6. Did the event occur in the past independently of vaccination/tuberculin diagnostics (indicate whether a similar AEFI occurred in the vaccinee and family in the past independently of immunization)	Yes*/No/Unknown/NA	Remarks
7. Was the patient in whom immunization/tuberculin diagnostics were conducted taking any medicinal product prior to vaccination/ tuberculin diagnostics (indicate whether vaccinee took any medicinal product in day of vaccination since AEFI may be the result of use of medicinal product as well as vaccine)	Yes*/No/Unknown/NA	Remarks
8. Is there a biological plausibility that the vaccine could cause the AEFI (indicate whether AEFI are similar to the natural course of the infection including the results of laboratory, instrumental studies as additional qualifying factor)	Yes*/No/Unknown/NA	Remarks

*In case of positive response give clarification in “Note” column.

Step 3. Algorithm of determination of causal association between serious and cluster of AEFI and use of vaccine and tuberculin


C. Inconsistent causal association between AEFI and use of vaccine, tuberculin
C1. Causal event
yes
I. Is there strong evidence for other causes?
no
II. Is there a known causal association between the development of AEFI and use of vaccine, tuberculin?
yes
IV. A2. Vaccine, tuberculin manufacturing failures-related reaction
yes
III. Was AEFI within the time window specific for this vaccine, tuberculin?
yes
A. Consistent causal association between AEFI and use of vaccine, tuberculin
A1. Vaccine, tuberculin properties-related reaction
no
C. Inconsistent causal association between AEFI and use of vaccine, tuberculin
C1. Causal event
yes
no
IV. Is there strong evidence against causal association between AEFI and use of vaccine, tuberculin?
yes
A. Consistent causal association between AEFI and use of vaccine, tuberculin
A2. Vaccine, tuberculin manufacturing failures-related reaction
A3. Programme error-related reaction
A4. Immunization, tuberculin diagnostics anxiety-related reaction
no
V. Other factors to differentiate between AEFI and use of vaccine, tuberculin
no
D. Unclassifiable AEFI
yes
Is a causal association between AEFI and use of vaccine, tuberculin classifiable?
no
B. Indeterminate AEFI
B1. Temporary relationship is consistent but there is insufficient definitive evidence for vaccine, tuberculin causal association (may be new vaccine, tuberculin linked event)
B.2 Other factors do not allow to differentiate between AEFI and use of vaccine, tuberculin
no
C. Inconsistent causal association between AEFI and use of vaccine, tuberculin
C1. Causal event

Step 4. Categories of causal association between serious and/or cluster of AEFI and use of vaccine, tuberculin according to step 3 algorithm of determination

Adequate information available	☐A. Consistent casual association between AEFI and use of vaccine/tuberculin ☐A1. Vaccine, tuberculin properties-related reaction ☐A2. Vaccine, tuberculin manufacturing failures-related reaction ☐A3. Programme error-related reaction ☐A4. Immunization, tuberculin diagnostics anxiety-related reaction	B. Inconsistent causal association between AEFI and use of vaccine/tuberculin ☐B1. Temporary relationship is consistent but there is insufficient definitive evidence for vaccine, tuberculin causal association (may be new vaccine, tuberculin linked event) ☐B2. Other factors do not allow to differentiate between AEFI and use of vaccine, tuberculin	C. Inconsistent causal association between AEFI and use of vaccine/tuberculin ☐C1. Causal event
Adequate information not available	☐D. Unclassifiable causal association between AEFI and use of vaccine, tuberculin Indicate the reasons why classification of causal association is impossible, specify additional information required for classification _____		

Summarize the classification of causal association between serious and/or cluster of AEFI and use of vaccine, tuberculin logic:_____.

With available evidence regional/central group of quick response could conclude that
(underline the appropriate)
the classification of causal association is_____

because:_____
_____
_____
_____
_____

Head of Group_____ _____ _____

(full name) (signature) (date)