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GUIDELINE ON EPIDEMIOLOGICAL DATA ON BLOOD TRANSMISSIBLE INFECTIONS

For inclusion in the Guideline on the Scientific data requirements for a Plasma Master File (EMEA/CPMP/BWP/3794/03)

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GUIDELINE ON EPIDEMIOLOGICAL DATA ON BLOOD TRANSMISSIBLE INFECTIONS

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1. PURPOSE

The requirement to collect epidemiological data on blood transmissible infections is intended to obtain information on the infection risk in a specific donor population and is thus an essential part of the measures taken to ensure an adequate selection of donors of blood and plasma. The purpose of these data is to characterise the donor population with respect to infection risk, and to allow comparison of risks between donor populations of individual collection centres. This is one of the measures to ensure that donations do not come from donors with a high probability of being infected with blood transmissible agents. Continuous epidemiological evaluation at individual blood/plasma collection centres together with an annual update of the assessment are therefore required.

Data on incidence and prevalence of transfusion transmissible infectious markers in donors of blood and blood components are also required as part of the annual reports of blood establishments (Annex II of Directive 2002/98/EC[1]).

This guideline will be kept under review in the light of experience with its use and any future EU requirements and guidance relevant to its content.

2. INFECTIOUS DISEASE MARKERS

Epidemiological data should be collected on those blood-borne infectious agents for which a potential transmission by blood products is well recognised and routine testing of blood and plasma donations is mandatory. These infectious agents currently include human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). The basic parameters of these testing requirements will therefore also apply to the collection of epidemiological data. Currently the minimum data collected cover anti-HIV 1 / 2, anti-HCV and HBsAg test results. The Plasma Master File (PMF) holder should also report separately the results of additional screening tests (e.g. NAT assays or anti-HBc). Clearly, a donor tested positive for a specific virus by both serological and NAT tests should be reported as a single case according to the relevant definition below.

Only confirmed infections should be reported using the following definitions[a]:

Confirmed seropositive	Repeatedly reactive (= 2 times reactive) in a screening test and positive in at least one supplementary test based on a different principle.
NAT only positive	Positive in a NAT assay for a specific virus (HIV, HCV or HBV), not found seropositive for that virus in serological screening, and shown to be true positive by separate NAT or later serology.

"NAT only positives" are in most cases indicative of recent infection and should, therefore, be reported separately from "Confirmed seropositives". Donations that are reactive in the initial screening tests but negative or indeterminate in confirmatory tests, should not be included as positives. Reporting of confirmed cases will reflect truly positive donors/donations rather than limitations in the specificity of the testing system. If donors are excluded from the donor population on the basis of a positive NAT test without a confirmatory test being performed, these data should also be reported, but separately from the data on confirmed positives. In all cases the companies should clearly explain their approach and criteria for excluding donors.

Further practical details for reporting data are set out in Section 5.

[a] The Council of Europe Questionnaire on the collection, testing and use of blood and blood products in Europe uses similar definitions.[2]

3. DONOR CLASSIFICATIONS

The Council Recommendation on the suitability of blood and plasma donors and the screening of donated blood in the European Community (98/463/EC)[3] provides the following definitions of types of donors:

Prospective donor	Someone who presents himself/herself at a blood or plasma collection establishment[b] and states his/her wish to give blood or plasma.
First time donor	Someone who has never donated either blood or plasma.
Repeat donor	Someone who has donated before but not within the last two years in the same donation centre.
Regular donor	Someone who routinely donates their blood or plasma (i.e. within the last two years), in accordance with minimum time intervals, in the same donation centre.

It is not the aim to gain information for epidemiological investigations based on the intention to donate or based on the presence of a donor in the collection centre without being tested. In order to get information on the prevalence and incidence of viral infections in the donor populations of individual collection centres, a test result for the viruses of interest needs to be available. Therefore, for the purpose of the assessment of epidemiological data of donor populations, the following definitions are used in this document[c]:

First time tested donor	Person whose blood/plasma is tested for the first time for infectious disease markers (with or without donation) without evidence of prior testing in a given blood system.
Repeat tested donor	Person whose blood/plasma has been tested previously for infectious disease markers in a given blood system.

A given blood system means a system that has records of whether a donor has donated before and the results of previous testing.

4. PREVALENCE AND INCIDENCE

This section first describes the general concepts of incidence and prevalence for infectious diseases and then the application of these concepts in the study of blood and plasma donors.

Prevalence and incidence can be defined as follows:

Prevalence	Rate of infection identified (including both past and present infections) at a specified point in time or over a specified time period in a defined population.
Incidence	Rate of newly acquired infection identified over a specified time period in a defined population.

Incidence is the measure of new infections and prevalence is a measure of the extent of infection in a population.

[b] Blood establishments are defined in Directive 2002/98/EC [1] as "any structure or body that is responsible for any aspect of the collection and testing of human blood or blood components, whatever their intended purpose, and their processing, storage and distribution when intended for transfusion. This does not include hospital blood banks." The use of the term "collection centre" in this guideline means a specific site where blood/plasma is collected, including any associated mobile sites.

[c] Similar definitions are used in the Council of Europe Questionnaire on the collection, testing and use of blood and blood products in Europe.[2]

Prevalence and incidence are complementary in that they provide information on past and current risk of infection in the population. High prevalence and incidence is indicative of established infection with continuing transmission. High prevalence and low incidence is indicative of established infection but with intervention measures (e.g. education on risk of infection, effective therapy) having been introduced. Low prevalence and high incidence indicates infection which is probably recently introduced into the population. Low prevalence and incidence would indicate that there is little or no evidence of past or current infection. Clearly while the first and third scenarios could be considered to be a high risk population, and the 4th scenario would indicate a low risk population, high prevalence and low incidence may be medium risk since established infection may create a reservoir from which future new infections (incidence) may arise.

There are certain characteristics of the blood/plasma collection system that need to be taken into account when parameters are defined for the collection of epidemiological data.[4-10] Prevalence data in donors tested for the first time provide information on the population presenting to become blood/plasma donors and who have not deferred themselves through the donor questionnaire. Determination of incidence is important because newly infected donors who are in the "window phase" (i.e. donors whose recent infection is not recognised by the applied tests) may donate potentially viraemic blood or plasma.

Prevalence in the context of the study of a donor population can be defined as:

$$\frac{\text{No. of positive donors in a specified period}}{\text{Total No. donors in the same specified period}}$$

This is often expressed per 100,000 donors. Since prevalence in "first time tested donors" is known to be different to prevalence in "repeat tested donors", it is recommended that these are reported separately (see Section 5).

Incidence in the context of the study of a donor population can be measured in "repeat tested donors" as:

$$\frac{\text{No. of donors who had a negative test result followed by a positive test result in the study period}}{\text{The sum of the time between the first and the last test result of every donor during the study period (person-years)}}$$

This is often expressed per 100,000 person-years. In the case of HBsAg an adjustment is needed to get an estimation of true incidence where donation is infrequent as an HBsAg positive may be missed.

However, in practice, the data required to determine incidence according to the above definition are difficult to obtain, because the intervals between the first and last donation/test sample of every individual donor during the study period have to be known for a large numbers of donors.

An alternative approach is to estimate incidence as follows:

$$\frac{\text{No. of donors who had a negative test result followed by a positive test result in the study period}}{\text{The total No. of donors who were tested more than once in the study period}}$$

However, this information is not readily available and, therefore, section 5 outlines a slightly modified approach to estimating incidence.

Incidence in "first-time tested donors" for HIV can be estimated using a sensitive/less-sensitive-test approach[6], where newly acquired infections are identified on the basis of a positive result with a sensitive test and a negative result with a less sensitive serological test. A modification of this approach uses NAT as the sensitive test, both for HIV and HCV[8].

Note: Estimates of prevalence and incidence are based on numbers of donors and not donations. Rates expressed in terms of donations are influenced by the donation frequency and by the fact that donors who remain negative will have more donations than those who become positive. The following simple example illustrates the influence of donation frequency:

If the incidence of an infection is 1 donor in 5 donor years (e.g. 5 donors are studied for 1 year and 1 of these donors develops an infection at the end of the year), the rate expressed as positive donors per total number of donations is illustrated below:

Frequency of donation	5 donors, 2 donations each	5 donors, 10 donations each	5 donors, 100 donations each
No. of +ve donors /Total No. of donations	1 in 10	1 in 50	1 in 500

5. RECOMMENDATIONS FOR REPORTING OF DATA ON INFECTIOUS DISEASE MARKERS

In reporting epidemiological data it is important to clearly describe the testing result definition and the classification of the donor as this will affect the results obtained and the comparability of data.

For each organisation responsible for collecting blood or plasma, the donor population which actually donates into the plasma pool should be described including information on how many donations are collected on average from one donor per year (frequency of donations), and on whether donations from first time tested donors are used in plasma pools.

As a result of the screening programme, a donor might be defined as "positive" for a certain virus based on different approaches (e.g. repeatedly reactive (= 2 times reactive) in a screening test, confirmed seropositive, NAT only positive, or NAT positive but not confirmed by follow-up investigations). Only "confirmed seropositives" and "NAT only positives" should be reported. NAT only positives should be reported separately from serological testing results, as outlined in Tables 1 and 2 in the Appendix. If confirmatory testing has not been done (e.g. following NAT reactive results) these data should be reported separately. (See also Section 2 of this guideline.)

The potential risk for plasma-derived products arises from undetected viraemic donations entering the plasma pool. A viraemic donor may donate once or several times during the "window period", i.e. the period of infection when the infected (and viraemic) donor is tested negative by screening tests. Therefore, in order to facilitate the risk assessment (see section 7 below), collection centres should report the number of donations collected as well.

Data should be reported using the tabular formats given in Tables 1 and 2 in the Appendix, per country, per organisation and per centre. The data should be reported for the calendar year (January – December). In order to facilitate a relative assessment of these data, the data should be presented in absolute numbers and calculated per 100,000 donors.

5.1 "First time tested donor" population

According to the definition in Section 3, "first time tested donors" are persons who are tested for the first time (with or without donation) and without evidence of prior testing in a given blood system. For companies using the applicant/qualified donor system[d], the "first time tested donor population" represents a sub-set of "applicant donors" (i.e. "applicant donors" that are tested for the first time in a given system).

Prevalence in "first time tested donors" in a specified period:

[d] **Qualified donor**: Individuals who have been qualified for continued donations by passing two donor screenings and two sets of serological viral testing for HIV, HBV and HCV within six months, with a minimum interval between the screenings according to national recommendations or requirements. **Applicant donor:** A donor going through the testing to become a qualified donor. Donations from an applicant donor are held in quarantine until cleared by an acceptable qualifying donation.

$$\frac{\text{No. of positive “first time tested donors” in a calendar year}}{\text{Total No. of “first time tested donors” in the same calendar year}}$$

5.2 “Repeat tested donor” population

As described in Section 3, a “repeat tested donor” is a person whose blood/plasma has been tested previously for infectious disease markers in a given blood system. This includes “regular donors” and “repeat donors”. For companies using the applicant/qualified donor system, this includes “applicant donors” tested for a second time, “applicant donors” requalifying after an interval of 6 months or more, and “qualified donors”.

Rate of positive “repeat tested donors” in a given period [e]

$$\frac{\text{No. of positive “repeat tested donors” in a calendar year}}{\text{Total No. of “repeat tested donors” in the same calendar year}}$$

Important note: The previous test result does not have to be in the same calendar year (e.g. a donor that only donates once during the calendar year would be included provided that the donor’s blood/plasma has been tested at some time in the past in the given blood system).

Positives detected in “repeat tested donors” will consist of a mixture of old infections that have not been detected previously because there has been a long period since the last donation, and new infections. As described in Section 4, it is important to estimate incidence because high incidence increases the probability that the donor population will include newly infected persons who may donate during the “window period”, when infection has taken place but is not detectable through routine screening tests. In order to estimate incidence, it is recommended to perform a subgroup analysis of the positive “repeat tested donors” in a calendar year (from the positive rate above) using the following formulae:

$$\frac{\text{No. of positive “repeat tested donors” in a calendar year, who had a negative test in a two-year period preceding the positive donation } [f]}{\text{Total No. of “repeat tested donors” in the same calendar year}}$$

If possible, the following should also be reported:

$$\frac{\text{No. of } \textbf{additional} \text{ positive “repeat tested donors” in a calendar year, who were identified as having recent infections from laboratory results and/or clinical history}}{\text{Total No. of “repeat tested donors” in the same calendar year}}$$

[e] This is not strictly prevalence of infection in the population because as soon as an infection is detected, the donor is excluded from the population.

[f] A two year period allows for the time interval that may occur between donations even in a “regular donor”.

6. EPIDEMIOLOGICAL ASSESSMENT OF DONOR POPULATIONS, AND TRENDS OVER TIME

The criteria used by the PMF Holder to establish acceptable ranges for epidemiological data, and to identify any individual blood/plasma collection centres reporting data above the acceptable range, should be described. The results of the analysis should be provided and information given on the action taken when any collection centre is outside of the acceptable range.

A comparison should be made with the data provided over the three previous years of reporting. The purpose is to identify any overall trends in the rates of infectious markers in the donor population. In addition, the effectiveness of remedial action for collection centres, which have previously been identified as above the acceptable range, should be described.

If formal epidemiological studies have been carried out in the donor population, the results should be provided including information on the methodology used, and trends over time discussed.

7. ESTIMATION OF THE RESIDUAL RISK

The approach used by the PMF Holder to estimate the risk of missing viraemic donations that may enter the production pool should be described. If donations from first time tested donors are used this should be included in the estimation of the risk. The estimated residual risk should be reported and discussed as part of the overall safety strategy as described in Section 1.2 of the Guideline on the Scientific Data Requirements for a Plasma Master File (PMF) EMEA/CPMP/BWP/125/04.

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transfusion-transmitted viral infections in France between 1992 and 2000. Transfusion 2002; 42: 980-988.

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APPENDIX: TABULAR FORMAT FOR THE REPORTS ON EPIDEMIOLOGICAL DATA

1. "First time tested donor" population

Results of NAT testing without confirmation and results of additional screening tests such as anti HBc should each be reported separately using an adapted copy of the tabular format below.

Calendar year:	No of donors tested in the given period (A)	HIV			HCV			HBV		
		No of positive donors		HIV Rate per 100 000 donors (B+C)/A x 100 000	No of positive donors		HCV Rate per 100 000 donors (D+E)/A x 100 000	No of positive donors		HBV Rate per 100 000 donors (F+G)/A x 100 000
		HIV 1/2 Antibody (B)	HIV 1 NAT only (C)		HCV Antibody (D)	HCV NAT only (E)		HBsAg (F)	HBV NAT only (G)	
Country 1										
Organisation A responsible for collecting										
Centre 1										
Centre 2										
Summary of Organisation A										
Organisation B responsible for collecting										
Centre 1										
Centre 2										
Summary of Organisation B										
Summary per country										

2. "Repeat tested donor" population

Results of NAT testing without confirmation and results of additional screening tests such as anti HBc should each be reported separately using an adapted copy of the tabular format below.

Calendar year :	No of donors tested in the given calendar year (A)	No of donations in the given calendar year (B)	Donation frequency[g] (B/A)	HIV			HCV			HBV		
				No of positive donors		HIV Rate per 100 000 donors (C+D)/A x 100 000	No of positive donors		HCV Rate per 100 000 donors (E+F)/A x 100 000	No of positive donors		HBV Rate per 100 000 donors (G+H)/A x 100 000
				HIV 1/2 Antibody (C)	HIV 1 NAT only (D)		HCV Antibody (E)	HCV NAT only (F)		HBsAg (G)	HBV NAT only (H)	
Country 1												
Organisation A responsible for collecting												
Centre 1												
Centre 2												
Summary of Organisation A												
Organisation B responsible for collecting												
Centre 1												
Centre 2												
Summary of Organisation B												
Summary per country												

[g] In cases where there are two sub-sets of donors (plasmapheresis and whole blood), give the frequency of donation separately for the two sub-sets.