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Research Ethics and International Epidemic Response: The Case of Ebola and Marburg Hemorrhagic Fevers

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Outbreaks of filovirus (Ebola and Marburg) hemorrhagic fevers in Africa are typically the theater of rescue activities involving international experts and agencies tasked with reinforcing national authorities in clinical management, biological diagnosis, sanitation, public health surveillance and coordination. These outbreaks can be seen as a paradigm for ethical issues posed by epidemic emergencies, through the convergence of such themes as: isolation and quarantine, privacy and confidentiality and the interpretation of ethical norms across different ethnocultural settings. With an emphasis on the boundaries between public health investigations and research, this article reviews specific challenges, past practices and current normative documents relevant to the application of ethical standards in the course of outbreaks of filovirus hemorrhagic fevers. Aside from commonly identified issues of informed consent and institutional review processes, we argue for more clarity over the specification of which communities are expected to share benefits, and we advocate for the use of collective definitions of duty to care and standard of care. We propose new elaborations around existing normative instruments, and we suggest some pathways toward more comprehensive approaches to the ethics of research in outbreak situations.

Introduction

The growing field of public health ethics expands the traditional scope of medical ethics, to include the community dimension of health and diseases alongside considerations over individual rights (Charlton, 1993; Dawson and Verweij, 2008). It also accommodates new debates attempting to define which community perspective (e.g., local versus global) should prevail. In this respect, public health interventions to control communicable diseases pose specific ethical questions, a number of which have been given renewed attention on the occasion of epidemics of international concern. Three recent examples come to the mind. First, the SARS pandemic of 2003 has created circumstances whereby a set of key ethical values in general (Singer *et al.*, 2003) and the duty to care in particular (Ruderman *et al.*, 2006) have come back to the fore in public health debates. Second, the emergence of XDR-tuberculosis has revived public health, ethical and legal debates around quarantine, isolation or involuntary confinement (Singh *et al.*, 2007). Third, the current epizootic of avian influenza (AI) H5N1 and the pending threat of a new pandemic have revealed tensions between industrialized and developing countries over ownership of biological samples shared through established international surveillance mechanisms. The latter case has been openly debated following a controversy between Indonesia and the World Health Organization (WHO), raising a number of interpretative issues around international laws and regulations (Fidler, 2008). The ethical dimension of this controversy is equally important to consider, although it has been given less emphasis so far. In trying to settle this debate, WHO experts have appealed to adherence to the principles of solidarity and reciprocity (WHO, 2007a).

Marburg and Ebola hemorrhagic fevers (filovirus hemorrhagic fevers, FHF) are emblematic of the concept of 'emerging diseases' (King, 2002). FHF outbreaks have been detected recurrently in sub-Saharan Africa since 1976, leading generally to a public health response of international dimensions. The peculiar features of these diseases, their circumstances and the international public

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health response that they trigger, all concur to the convergence within a same outbreak event of unique ethical issues, including the ones encountered with SARS, XDR-TB and AI. An added level of complexity with FHF is the usual involvement of remote, underserved and culturally distinct populations as the main victims of these outbreaks. We argue that FHF outbreaks represent a case in point for further research, debates and guidelines covering ethical issues posed by epidemics in particular, and public health emergencies in general. In this article, we try to answer a number of questions raised in particular by medical actors involved in emergency rescue to victims of FHF, and we focus on the distinction between field epidemiology research and public health investigations.[1] After an overview of relevant features and circumstances of FHF outbreaks, we examine how field research has so far taken place in these contexts, and how it has created tensions between clinical practitioners and researchers. We review normative documents expected to address the case of research ethics during epidemic emergencies, and we consider the particular problems posed by the collection of biological specimens. Next, through a review of the biomedical literature, we compile and analyze statements illustrating how ethical issues have been addressed during past FHF outbreaks. Beyond common concerns over informed consent and research ethics committees, we argue for future debates to include questions of benefit sharing, as well as collective definitions of duty to care and standards of care. We then examine the limitations of existing norms in helping delineate the boundaries between research and public health investigations. Similarly, we examine current specifications about waiving individual consent or ethics review processes. Finally, we advocate for a number of more fundamental conditions to be put in place, in order to properly address ethical tensions seen between care and research during outbreak events.

Filovirus Hemorrhagic Fevers: Origins, Features and Circumstances

Filoviruses were initially discovered after an outbreak of hemorrhagic fever in Marburg, Germany in 1967. Subsequent occurrences of FHF involving humans have been reported mostly in rural areas of sub-Saharan Africa,[2] with the first community outbreak identified in 1976 near the banks of the Ebola river in Zaire (current Democratic Republic of the Congo, DRC). Accordingly, the current nomenclature classifies filovirus isolates under species belonging to two related but distinct genera: Ebolavirus and Marburgvirus. All strains are highly transmissible through blood or bodily fluids. Outbreaks in sub-Saharan Africa are classically associated with high case fatality ratios, which can reach 90 per cent, depending on the virus species involved. A hallmark of FHF is nosocomial transmission, leading characteristically to fatalities among health care personnel and additional disruption of the local health care system, especially during urban outbreaks (Formenty *et al.*, 2005).

No specific treatment, prophylaxis or vaccine is currently available. Outbreak control relies on contact tracing, case finding and isolation of suspect or confirmed cases.

Understandably, FHF outbreaks cause panic in affected communities and raise concerns over transnational spread. The public health response typically involves collaborations of national authorities with international agencies, the latter offering additional expertise and reinforcements for diagnostic procedures, patient care, infection control and epidemiological investigations. Compared to epidemics of similar or higher magnitude caused by other infectious agents, FHF occurrences generally induce the rapid mobilization on site of multiple international actors. The sensational and dramatic nature of FHF outbreaks has often been a point of attraction for members of the national or international press as well (Garrett, 2001). As witnessed in past outbreaks, some reporters or photographers were ready to convey images of diseased individuals and of afflicted communities, even when such images could be degrading to the victims or their communities. Beyond altruism, aid institutions can also be motivated by a range of perceptions, agendas or interests over the disease.[3] Under such combined circumstances, communities have sometimes reacted with distrust, hostility and even violence toward outbreak control teams and foreign investigators (Bausch *et al.*, 2007). Isolation in closely controlled hospital areas has naturally been felt as a further cause of distress for FHF patients. Their physical suffering is compounded by psychological trauma due to additional burdens, such as: expressions of ostracism by the community, lack of privacy, the constant proximity of the dead, restricted contacts with family members and limited or anonymous interactions with medical attendants wearing protective equipment (Bausch *et al.*, 2008). Finally, the universalistic biomedical model endorsed by outbreak response teams can create incompatibilities with local cultural representations of the disease, an issue which has only recently been addressed with due care through the systematic involvement of medical anthropologists (Hewlett *et al.*, 2005).

Research and Public Health Investigations in FHF Outbreaks: The Main Questions

Field research activities have always been common and essential facets of any response to FHF outbreaks. This is understandable both in terms of the sustained scientific interest in emerging diseases since the 1980s, and of concerns over the international spread of agents with high lethality. Recent discoveries have opened promising paths toward possible curative and preventive interventions (Bausch *et al.*, 2008). However, field research on FHF has so far largely been limited to descriptive or analytical studies covering epidemiological, clinical and biological disciplines. Routine activities by outbreak investigation teams include the establishment of epidemiological databases, linked to the collection of clinical samples, typically blood samples from patients or contacts. Recent technical progress in laboratory procedures (Towner *et al.*, 2007) offer the possibility of rapid diagnostic testing of suspect cases in real time under field conditions. This is a major and most welcome improvement for clinicians in charge of triaging patients, as compared to past practices where serial samples used to be collected routinely and analyzed in distant reference laboratories without any guarantee that the procedure would benefit clinical management directly for these patients. However, the same uncertainties regarding the immediate benefit of blood testing to patients have resurfaced on the occasion of the latest FHF outbreak in Bundibugyo (Uganda). A new species of Ebola virus was involved (WHO, 2008), raising questions over the interpretation of established tests and resulting in necessary adjustments to laboratory protocols (Towner *et al.*, 2008). While this has inevitably lead to delayed laboratory case confirmation, there is no doubt that the swift design of improved molecular techniques could potentially be of great benefit to communities living in the Bundibugyo area, and beyond. Unfortunately there have been recurrent tensions, mistrust and debates between research teams and clinicians in charge of patients, mostly about the dual use (diagnostic versus research) of patients' samples and the relevance of iterative testing to combine diagnostic and research considerations. This has often put local health authorities and humanitarian organizations in an odd position, whereby individual patients' care and public health response had to accommodate unsolicited but implicit participation in research activities without prior agreement on relevance, feasibility and ethical safeguards. Central to these debates are two critical questions. First, what are the boundaries between research and public health investigations in the context of FHF outbreaks? Second, to what extent do emergency circumstances justify derogations or particular regimes in the application of common ethical standards of research? For example, provisions for informed concern are essential considerations. In the context of investigations regarding an FHF outbreak, however, several difficulties coexist. Patients are kept in isolation (voluntary or forcible), and their condition is generally critical. Clinicians and field researchers are not in favorable conditions either: they typically have different cultural or linguistic backgrounds, and wear protective barriers under which nonverbal communication is considerably limited. All these circumstances concur to enhance a sense of power asymmetry between researchers and patients, and compromise the patients' capacity to make free, conscious and genuinely informed choices over their clinical management and their involvement in research activities. By all standards, and specifically by the criteria that they have an 'identifiably increased likelihood of incurring additional or greater wrong' (Hurst, 2008), FHF patients are thus unusually vulnerable and deserve special protection.

Available Guidelines, Regulations and Conventions

National Regulations: The US 45 CFR 46 and Its Interpretation

Partly for historical reasons, experts from US institutions in general, and from the US Centers for Disease Control and Prevention (CDC) in particular, have regularly and extensively contributed to outbreak investigations and responses during FHF occurrences, and to the generation of important scientific advances in this area. It is therefore important to consider under which regulations they have been operating during fieldwork on foreign territories. The reference document is the US Code of Federal Regulations, title 45 (public welfare), part 46 (protection of human subjects) (Department of Health and Human Services, United States of America, 2007). Sub-part A of 45 CFR 46 was endorsed by 17 US government agencies and is known as the 'Common Rule', defining the federal policy for the protection of human research subjects. Its scope explicitly covers activities on foreign territories, as indicated by the mention of 'research conducted, supported, or otherwise subject to regulation by the Federal government outside the United States'. Importantly, research is defined as activities '. . .designed to develop or contribute to generalizable knowledge'. The CDC Human Research Protection Office (HRPO) provides interpretations and clarifications of this definition, allowing the

distinction between 'public health research' and 'public health non-research' (Centers for Disease Control and Prevention, United States of America, 1999). The key qualification in determining this distinction lies in the primary intent of the activity. MacQueen and Buehler (2004) illustrate with case studies (including tuberculosis outbreak in a prison) some applications of the HRPO interpretation of the Common Rule. Classification of activities as research has important implications, among others the need for qualified oversight by an institutional review board (IRB) or research ethics committee (REC).[4] The primary intent principle has limitations, however. For example, to be credible, intents need to be specified in advance of potentially harmful activities, especially when very similar or identical activities are underpinned by different intents. This would imply the existence of independent bodies or agencies capable to record expressed intents ahead of the implementation of activities, a rather unrealistic proposal when applied to fast evolving emergency settings.

Through further elaborations on the concept of generalizable knowledge, the HRPO guidelines provide additional clarifications, which are of particular relevance to the case of FHF outbreaks. In particular, a number of interpretative comments to the Common Rule offer useful guidance on three problematic issues: post hoc investigations, the mix of research and non-research and storage of biological samples for dual use. These comments are worded respectively in the following terms:

> A non-research project may generate generalizable knowledge after the project is undertaken even though generating this knowledge was not part of the original, primary intent. In this case, since the primary intent was not to generate or contribute to generalizable knowledge, the project is not classified as research at the outset. However, if subsequent analysis of identifiable private information is undertaken to generate or contribute to generalizable knowledge, the analysis constitutes human subjects research that requires IRB review.
>
> If a project includes multiple components and at least one of those components is designed to generate generalizable knowledge, then the entire project is classified as research unless the components are separable.
>
> Most emergency responses tend to be non-research because these projects are undertaken to identify, characterize, and solve an immediate health problem and the knowledge gained will directly benefit those participants involved in the investigation or their communities. However, an emergency response may have a research component if: 1) samples are stored for future use intended to generate generalizable knowledge or 2) additional analyses are conducted beyond those needed to solve the immediate health problem.

These interpretative comments from the HRPO imply that additional sampling or the storage of specimens to carry deferred analysis with a purpose going beyond solving immediate health needs can be qualified as research and require review by an IRB. An exception to the latter requirement could be waived if identifiable private information is erased. This is generally impractical with FHF outbreaks, considering the need to match separate databases accurately and the obligation to communicate results to concerned individuals.

In general, the interpretative instruments reviewed above are based on a national legal principle (the Common Rule). They cannot be claimed as universal principles until they have been reviewed and endorsed by organizations with internationally recognized normative mandates.

Council for International Organizations of Medical Sciences (CIOMS)

With the recently issued 'International Ethical Guidelines for Epidemiological Studies' CIOMS (2008) is the only international organization to venture substantially in the territory of ethics and emergencies, and to issue some concrete guidance that could be applied to epidemic emergencies. First, in its Introduction, CIOMS elaborates on the distinction between 'research' and 'practice', and recognizes difficulties in applying the 'generalizable knowledge' definition to the field of epidemiology. Second, among commentaries to Guideline 2 ('Ethical review committees'), CIOMS considers specifically the case of research in emergency situations, including disease outbreaks. It sees as best practice the principle: 'to establish the basic research design for various categories of research prior to the emergency', allowing 'prior ethical review of at least the major features of the research design'. Along the same line, Bausch *et al.* (2008) have recently proposed operational strategies in anticipation of future interventional research on FHF, including provisions for proper and timely ethical reviews. Third, commentaries to Guideline 4 ('Individual informed consent') set out a number of situations whereby waiving consent would be acceptable in epidemiological studies. Listed conditions include: minimization of risk; anonymization of samples; impracticability to locate persons whose samples or records are to be examined; or studies 'which are carried out under legislative or regulatory authority for public health, such as disease surveillance'. It is not clear from

Guideline 4 if systematic blood sampling of suspect FHF cases or otherwise exposed persons would fall within the definition of 'disease surveillance'. However, Guideline 24 ('Use of stored biological samples and related data') and commentaries make it clear that the constitution of sample repositories and their secondary use are subject to individual consent and submission to an ethical review committee.

Overall, it appears that the recent CIOMS 'International Ethical Guidelines for Epidemiological Studies' are more specific, more encompassing and more restrictive than their precursor 'International Guidelines for Ethical Review of Epidemiological Studies' (CIOMS, 1991).

Declaration of Helsinki

The sixth revision of the Declaration of Helsinki (World Medical Association) sets out general principles, and does not specifically address the case of emergencies. In line with CIOMS's 2008 guidelines, Section 25 of the Declaration recognizes that 'there may be situations where consent would be impossible or impractical to obtain . . .' for 'research using identifiable material or data . . .', and that 'in such situations the research may be done only after consideration and approval of a research ethics committee.'

Part C of the Declaration addresses in broad terms the question of research combined with medical care, with an obvious focus on interventional research. Two sections (33 and 34) elaborate on information to patients, and have implicit relevance to epidemiological research as well. Patients should be informed at the outset of the intervention on 'which aspects of the care are related to the research' (Section 34), and at the conclusion of the study about the outcome (Section 33).

Revised (2005) International Health Regulations

Since many public health experts working in the field of outbreak response would naturally turn to the revised (2005) IHR to seek guidance, it is important to emphasize the considerable limitations of this landmark document when it comes to ethical issues. Provisions of the revised (2005) International Health Regulations (WHO, 2005a) do not refer explicitly to ethical concepts, but to a number of human rights considerations (Fidler, 2005) concerning restrictions and other measures imposed upon travelers. Regrettably, the (2005) International Health Regulations fail to elaborate on which ethical standards apply during public health surveillance, outbreak investigations and outbreak responses (Calain, 2007). An exception might be found in Article 45, which covers questions of confidentiality in the 'Treatment of personal data', but without specifying the exact circumstances (control of travelers or local outbreak investigations) when these would apply.

The case of FHF shows the diversity and complexity of ethical problems that typically arise during outbreaks of communicable diseases. Emergency circumstances can lead to a blurring of limits between public health practice and research, both because of time constraints and because this limit is sometimes genuinely difficult to define. There is a deficit in international guidance about ethical issues arising during the practice of research in emergencies in general, and outbreaks in particular. In this respect, the ethical standards referred to in the WHO 'Guiding principles for international outbreak alert and response' (WHO, 2005b)[5] fall within a regulatory vacuum. As reviewed in the previous sections, normative documents currently applicable are mostly limited to the US 'Common Rule' and to the CIOMS 'International Ethical Guidelines for Epidemiological Studies'. The former is a national regulation, whereas the latter is still a provisional text and it has no regulatory power. Together, both documents cover to some extent a number of issues relevant to epidemic emergencies, such as: informed consent, ethics review mechanisms, collection and storage of biological samples, and community engagement. Both appropriately posit the distinction between research and public health practice as a first step in the identification of ethical arguments, but they fail to explore exhaustively the full scope of ethical issues triggered by the qualification of an intervention as 'research'.

Collection and Storage of Biological Specimens

The collection of biological specimens in FHF outbreaks generally entails venipuncture to sample serum for virological isolation or detection, or for serological diagnostic. Under usual medical circumstances, venipuncture cannot be considered as totally innocuous. Rare complications such as nerve damage or asystole due to vasovagal reactions have been described. Significant blood losses leading to anemia can result from repeated sampling, particularly during intensive care circumstances. The fact that venipuncture is not an absolutely benign act is implicitly recognized through an interpretative document to a provision of the Common Rule for expedited ethics review (Department of Health and Human Services, Office for Human Research Protections, United States of America, 1998), specifying acceptable volume and frequency thresholds to the collection of blood samples. In FHF isolation wards, the above-mentioned risks

are probably enhanced. Moreover, for FHF victims, any venipuncture implies potentially creating an additional source of prolonged bleeding, a minor complication in itself but certainly an extra physical and psychological discomfort under the circumstances. Thus, venipuncture obviously does not fit among 'minimal risk' procedures considered under commentaries to Guideline 4 of CIOMS (2008) with regard to conditions for waiving consent.

Cultural perceptions and anthropological representations about blood and tissue sampling in countries affected by FHF represent an added complexity, and can be either under- or overestimated. In Bundibugyo (Uganda) for example, Carole Coeur (2007) describes the use of body samples for witchcraft practices. Blood is sometimes exchanged to symbolize close personal links between individuals and skin samples from cadavers can allegedly be used for divination or sacrifices. In such contexts, autopsies, post-mortem sampling,[6] and even blood sampling obviously have deep significance for communities. On the other hand, when research subjects in Uganda were surveyed regarding the use of their blood samples, a vast majority were willing to contribute samples for research on any disease, including potentially stigmatizing ones such as HIV, and trusted IRBs to determine when tissue samples could be used for research purposes (Wendler *et al.*, 2005). The notion of informed consent thus covers a range of complexities, which are usually beyond the immediate understanding of foreign researchers working in emergencies.

Upshur *et al.* (2007) argue that taking tissue samples should entail community engagement in research oversight, in addition to individual-level consent. Processes for such 'community permission' have been described (Diallo *et al.*, 2005).

The question of storage of biological specimens is compounded by a number of additional considerations peculiar to agents of viral hemorrhagic fevers. The storage of infectious samples and strains of filoviruses require maximum security laboratories, resulting in a de facto monopoly by a limited number of reference facilities tasked with the management of official repositories and decisions about sharing specimens. The issue is obviously complicated by concerns over illicit use of the infectious agents, alleged risks of 'bioterrorism', and the potential for patent claims over nucleic acid sequences used for diagnostic procedures or research.

Past Practices in Field Research on FHF

In order to analyze how and to what extent ethical issues were considered during past FHF outbreaks, we systematically retrieved original peer-reviewed articles based primarily on clinical, epidemiological or biological investigations directly linked geographically with identified outbreaks (Table 1). Our primary data sources were two compilations of articles published in supplements of the *Journal of Infectious Diseases* in 1999 and 2007, respectively. To identify additional articles published outside of these supplements, a search restricted to English or French languages was done in PUBMED, using the following MeSH terms[7]: 'Hemorrhagic Fever, Ebola' and 'Marburg Virus Disease'.

We excluded single case reports, unlinked case series, review articles and comprehensive articles including a mix of historical or broad public health perspectives. Furthermore, only articles reporting primary activities on African territories were considered. Finally, only articles published later than 1995 were analyzed, due to a frequent lack of clarity or homogeneity about data sources in earlier papers.

Data from articles thus selected were extracted and compiled considering the following fields: year and site of the outbreak; scope of activities (epidemiological, clinical or biological); condition of surveyed individuals (asymptomatic, ill, convalescent, health worker, others); sampling of blood[8] or other tissues; mention of consent; mention of consultation of a REC; mention of any other consideration relevant to ethics.

We attempted to classify described activities as 'research' or 'non-research', using a simple algorithm that takes into account two criteria: (i) the primary intent (as defined in HRPO guidelines) and (ii) the existence of an incremental risk (physical, moral or psychological) for surveyed individuals. The concept of incremental risk has best been described in the literature on emergency medicine research, where it has been used to determine the acceptability of research risks (Weijer, 2004), and as one among possible criteria for waiving consent (Gray, 2001). In his argument about ethical 'component analysis', Weijer compares therapeutic and nontherapeutic procedures. He proposes that the incremental risk criterion should apply to nontherapeutic procedures, where a 'harm–benefit calculus' is deemed inappropriate. In the case of epidemic emergencies considered here, we use the existence rather than the magnitude of an incremental risk as one operational criterion in the qualification of field activities as research. For example, some activities that would not qualify as research according to the primary intent criteria (e.g., drawing blood samples for diagnostic purpose) might eventually relate to research if there exists an incremental risk relative to standard management (e.g., sampling larger quantities to calibrate tests of unknown reliability). This method of classification between 'research' and 'non-research' thus refines

Table 1. Mapping of ethics practices in Ebola and Marburg hemorrhagic fever outbreaks

Article reference	Year (intervention)	Site (country)	Scope of activities/ population concerned/ procedure(s)	Qualification	Consent sought, from whom; other relevant quotes *(verbatim)*	Research ethics committee(s) involved *(verbatim)*
Amblard *et al.* (1997)	1994	Makokou Hospital and Minkebe (Gabon)	Biological/I/V	Indeterminate	No mention	No mention
Baize *et al.* (1999)	1996	Mayibout and Booué (Gabon)	Biological/I, C, A/V	Research	"We obtained specimens from patients (with verbal informed consent) in two Ebola epidemics."	No mention
Baize *et al.* (2002)	1996	Mayibout and Booué (Gabon)	Biological/I, C, A/V	Research	"Several blood samples were taken with the patients' verbal informed consent during the course of the disease and during recovery, . . ."	No mention
Bausch *et al.* (2003)	1999	Durba and Watsa (DRC)	Epidemiological/A, HW/V	Research	"The rationale for conducting the study was explained to all participants." "For those persons who did not understand French, the questionnaire was administered by a local HCW in the appropriate language." "Participants were given a small bag of peanuts as a token of appreciation for their cooperation."	No mention
Bausch *et al.* (2006)	1998–2000	Durba and Watsa (DRC)	Clinical, biological and epidemio-logical/I, C, A/V, T	Research	No mention	No mention

(Continued overleaf)

Table 1. (Continued)

Article reference	Year (intervention)	Site (country)	Scope of activities/ population concerned/ procedure(s)	Qualification	Consent sought, from whom; other relevant quotes *(verbatim)*	Research ethics committee(s) involved *(verbatim)*
Bausch *et al.* (2007)	2000	Gulu Regional Hospital (Gulu, Uganda)	Epidemiological/I	Research	"Information consent was obtained from the patient or guardian"	No mention
Bertherat *et al.* (1999)	1999	Durba (DRC)	Epidemiological/I, A/V, T	Indeterminate	No mention	No mention
Bitekyerezo *et al.* (2002)	2000	Mbarara University Teaching Hospital (Uganda)	Clinical and epi-demiological/I, A/V	Non-research	No mention	No mention
Borchert *et al.* (2002)	1999–2001	Durba and Watsa (DRC)	Epidemiological/I, C/V, T	Non-research (research on one sample two years later)	No mention	No mention
Borchert *et al.* (2006)	1998–2000	Watsa sub-district (DRC)	Epidemiological/ A/V	Research	"We asked all contacts we met to give verbal informed consent; . . ."	"This study was approved by the ethics committee of the Antwerp Institute for Tropical Medicine and the representative of the Ministry of Health in Watsa."
Borchert *et al.* (2007)	2001–2002	Durba and Watsa (DRC)	Epidemiological/ HW/V	Research	"After giving informed consent, HWs were asked which patients . . ."	"This study was approved by the ethics committee of the Institute for Tropical Medicine in Antwerp, Belgium and by the local representative of the Ministry of Health in Watsa."

Boumandouki *et al.* (2005)	2003	Mbomo (Republic of the Congo)	Epidemiological/ I/V	Indeterminate	"Chaque cas suspect ou probable était évalué par une équipe médicale et, après consentement verbal, le sang était prélevé sur tube sec à la veine radiale. Aux patients qui refusaient la prise de sang, qu'ils considéraient comme une spoliation de leur intégrité vitale, nous avons proposé un prélèvement de salive . . .ou un prélèvement d'urine dans un pot."	No mention
Busico *et al.* (1999)	1995	Kikwit and the surrounding area (DRC)	Epidemiological/ A/V	Research	"Informed consent was obtained from all participants." "Each study participant who answered a one-page questionnaire and donated blood sample was offered either 22,000 zaires or a can of powdered milk." "No individual compensation was given; however, food staples intended for the entire village were donated to the chiefs of the participating villages."	No mention
Bwaka *et al.* (1999)	1995	Kikwit (Bandundu region, DRC)	Clinical/I/CV	Non-research	No mention	No mention
Colebunders *et al.* (2007)	1998–2000	Durba and Watsa (DRC)	Clinical/I/V	Non-research	No mention	No mention
Dowell *et al.* (1999)	1995	Kikwit and the surrounding region (DRC)	Epidemiological/I, C, A/V	Research	No mention	No mention

(Continued overleaf)

Table 1. (Continued)

Article reference	Year (intervention)	Site (country)	Scope of activities/ population concerned/ procedure(s)	Qualification	Consent sought, from whom; other relevant quotes *(verbatim)*	Research ethics committee(s) involved *(verbatim)*
Formenty *et al.* (2006)	2003	Kéllé and Mbomo (Republic of the Congo)	Biological/I, A/V	Research	"For diagnostic purposes, 9 of these patients (age, 28–75 years) provided verbal consent to provide both an oral fluid sample and a venous blood sample." "All patients but 2 gave verbal consent to provide both an oral fluid sample and a venous blood sample."	No mention
Francesconi *et al.* (2003)	2000	Gulu district (Uganda)	Epidemiological/I, A/	Research	"This study, the results of which are reported here, was fully integrated into the surveillance activities described above and was authorized by the director of the Gulu District Health Services and the Ugandan Ministry of Health."	No mention
Georges *et al.* (1999)	1994–1997	Northeastern Gabon	Epidemiological and biological/I, A/V	Research	"Informed consent was obtained from the patients or their parents or guardians."	No mention
Georges-Courbot *et al.* (1997a)	1996	Booué (Gabon)	Biological/I, A/V	Indeterminate	No mention	No mention
Georges-Courbot *et al.* (1997b)	1994, 1996	Gabon	Biological/I/V	Indeterminate	No mention	No mention
Hutchinson and Rollin (2007)	2000–2001	Gulu (Uganda)	Biological/I, A/V	Research	No mention	No mention
Khan *et al.* (1999)	1995	Bandundu region and Kikwit (DRC)	Epidemiological/I, A/V	Non-research	No mention	No mention

Kibadi *et al.* (1999)	1995	Kikwit (Bandundu region, DRC)	Clinical/I/V	Non-research	"These patients were chosen because they were easy to contact and willing to participate"	No mention
Ksiazek *et al.* (1999a)	1995	Kikwit (DRC)	Biological/I, C/V	Research	No mention	No mention
Ksiazek *et al.* (1999b)	Various	Various	Biological/I, O/V	Indeterminate	No mention	No mention
Leroy *et al.* (2000a)	1996	Gabon	Biological/I, C, O (patient with other infection)/V	Research	"Verbal consent was obtained, . . ."	No mention
Leroy *et al.* (2000b)	1996	Northern Gabon	Biological/A/V	Research	No mention	No mention
Leroy *et al.* (2001)	1996	Northern Gabon	Biological/A/V	Research	No mention	No mention
Leroy *et al.* (2002)	1996	Booué (Gabon)	Biological/I, A/V	Research	"Samples were obtained with the patients' verbal informed consent . . ."	No mention
Lucht *et al.* (2007)	2003	Mbomo and Mbanza (Republic of the Congo)	Biological/I, A/V	Research	No mention	No mention
Maruyama *et al.* (1999a)	1995	Kikwit (DRC)	Biological/C/V, BM	Research	"Informed consent was obtained from all donors. The study followed human experimentation guidelines of the US Department of Health and Human Services and Scripps Research Institute."	No mention
Maruyama *et al.* (1999b)	1995	Kikwit (DRC)	Biological/C/V, BM	Research	No mention	No mention

(Continued overleaf)

Table 1. (Continued)

Article reference	Year (intervention)	Site (country)	Scope of activities/ population concerned/ procedure(s)	Qualification	Consent sought, from whom; other relevant quotes *(verbatim)*	Research ethics committee(s) involved *(verbatim)*
Mupapa *et al.* (1999a)	1995	Kikwit General Hospital (Kikwit, DRC)	Clinical/I, C/V	Research	"Transfusions were given with patient consent or the consent of a family member if the patient had reduced consciousness." "Five convalescent patients, who had been discharged from the hospital between 2 and 15 May 1995, agreed to donate blood."	No mention
Mupapa *et al.* (1999b)	1995	Kikwit General Hospital (Kikwit, DRC)	Epidemiological and clinical/I	Non-research	No mention	No mention
Mupere *et al.* (2001)	2000–2001	Gulu and Lacor hospitals (Uganda)	Clinical and epi-demiological/I/V	Non-research	No mention	No mention
Ndambi *et al.* (1999)	1995	Mosango (DRC)	Epidemiological and clinical/I/	Non-research	No mention	No mention
Nkoghe *et al.* (2005a)	2001–2002	La Zadié, Ivindo, Mpassa, Oyem (Gabon)	Epidemiological/I, A/V, T	Indeterminate	"Chaque cas suspect était évalué par une équipe médicale et, après consentement verbal, le sang été prélevé sur tube sec à la veine radiale."	No mention
Nkoghe *et al.* (2005b)	2002	Haut Ogooué (Gabon)	Clinical and epi-demiological/I, A/V	Non-research	No mention	No mention
Onyango *et al.* (2007)	2004	Yambio (Sudan)	Biological/I/V	Indeterminate	"This study is based on an intervention after a suspected disease outbreak; therefore, consent was not required, as stipulated by the WHO guidelines."	No mention

Prehaud *et al.* (1998)	Various	Sera from Gabon, Zaire and Côte d'Ivoire	Biological/I, C, A/V	Research	No mention	No mention
Richards *et al.* (2000)	1996	Johannesburg (South Africa). Primary infection: Libreville (Gabon)	Clinical/I, C/V	Non-research	No mention	No mention
Rodriguez *et al.* (1999)	1995	Kikwit (DRC)	Biological/I, C/V	Research	"Informed consent was obtained from all patients included in this study. The study was performed according to guidelines of the US Department of Health and Human Services."	No mention
Roels *et al.* (1999)	1995	Kikwit (DRC)	Epidemiological/I, A/V	Research	No mention	No mention
Rollin *et al.* (2007)	2000	Gulu (Uganda)	Biological/I, A/V	Research	No mention	No mention
Rowe *et al.* (1999)	1995	Kwilu subregion of Bandundu region (DRC)	Clinical, biological and epidemio-logical/A, C/V	Research	"Informed consent was obtained from the participants or their guardians." "The convalescents who participated were given food packages at each visit as an incentive; convalescents and their families who participated in the 21-month follow-up visit were also given US$100. All convalescents who could be contacted were given a 1-month supply of iron and folate supplements, regardless of whether they chose to participate."	"The study was approved by the Institutional Review Board of the Centers for Disease Control and Prevention (CDC) US department of Health and Human Services; and the Ministry of Health of the former Zairian government." "The study protocol was approved by . . . , Bandundu region health authorities, . . ."

(Continued overleaf)

Table 1. (Continued)

Article reference	Year (intervention)	Site (country)	Scope of activities/ population concerned/ procedure(s)	Qualification	Consent sought, from whom; other relevant quotes *(verbatim)*	Research ethics committee(s) involved *(verbatim)*
Saijo *et al.* (2001)	1976, 1977, 1995 and undefined	DRC and undefined	Biological/I, A/V	Research	No mention	No mention
Sanchez *et al.* (1999)	1995–1996	Kikwit (DRC)	Biological/I/V, T	Indeterminate	No mention	No mention
Sanchez *et al.* (2004)	2000	Saint Mary's Lachor Hospital and a government hospital in Gulu (Uganda)	Biological/I, A/V	Research	No mention	No mention
Sanchez *et al.* (2007)	2000–2001	Gulu (Uganda)	Biological/I/V	Research	"In accordance with CDC institutional review board policies, all samples were anonymized and identified only as fatal and nonfatal cases."	No mention
Tomori *et al.* (1999)	1995	Kikwit and surrounding towns (DRC)	Epidemiological/A, HW/V	Research	"Informed consent was obtained from the participants in this research which was performed according to guidelines of the US Department of Health and Human Services in conjunction with the Ministry of Health, Democratic Republic of Congo."	No mention

Towner *et al.* (2004)	2000–2001	Saint Mary's Lachor Hospital and Gulu General Hospital (Uganda)	Biological/I, C/V	Research	"The epidemic . . .provided a rare opportunity to collect multiple specimens from patients throughout the course of the disease and to gain a better understanding of the clinical virology of Sudan ebolavirus . . ."	No mention
Towner *et al.* (2006)	2005, 1998, 1987	Uige (Angola), Durba (DRC), Kenya	Biological/I/V, T	Indeterminate	No mention	No mention
Towner *et al.* (2007)	2005	Uige (Angola)	Biological/I/V	Indeterminate	No mention	No mention
Villinger *et al.* (1999)	1995	Kikwit General Hospital (Bandundu region, DRC)	Biological/I, A/V	Research	No mention	No mention
Weidmann *et al.* (2007)	2005	Angola	Biological/I/V	Indeterminate	No mention	No mention
Zaki *et al.* (1999)	1995	Kikwit (DRC)	Biological/I/V, T	Research	No mention	No mention
Zhai J *et al.* (2007)	1995, 2000, 2005	Kikwit (DRC), Durba (DRC), Uige (Angola)	Biological/I/V	Indeterminate	No mention	No mention

Procedures
V, venipuncture.
T, tissue sampling from deceased patient.
BM, bone marrow sampling.
Condition of persons investigated
I, ill.
A, asymptomatic at the time of sampling.
C, convalescent.
O, others.
HW, health worker.

the interpretation of the Common Rule in the sense that it moves from a binary criterion (the primary intent) toward a double and sequential screen (primary intent first, then incremental risk). It should be noted that reference to the primary intent criterion is never explicit in the publications that we have reviewed. Our qualification is thus retrospective and based on our own judgment about circumstances and activities. Similarly, the incremental risk criterion is based on our own judgment and could be challenged as insufficiently informed from the limited amount of descriptions available in the reviewed articles. Given these limitations, however, a sequential screen provided an opportunity for crosschecking our classification, and thus capturing a greater number of published studies as research.

Some articles could not be unambiguously classified and were qualified as 'indeterminate'. Typically, difficulties to classify activities arose when neither primary intent nor incremental risks was clear from available descriptions, or when diagnostic laboratory methods could not be definitely ascribed as either recognized standards or investigative procedures. When the primary intent of venipuncture was diagnosis but researchers performed additional tests that were not relevant to the direct management of concerned patients (e.g., Sanchez *et al.* 2004, 2007), the studies were considered research, in accordance with HRPO guidelines.

In total 58 publications were selected, concerning at least 12 outbreaks covering the period from 1994 to 2007. With the exception of one paper reporting an attempt at therapeutic intervention using convalescents' blood, all studies were observational or descriptive. Venipuncture was mentioned as part of the intervention in 54 of the publications. Our own analysis lead to the qualification of reports as research in 34 cases, non-research in 11 cases and indeterminate in 13 cases. Among the 34 definite research interventions, individual consent was sought in 15 cases and consultation with an REC was mentioned in three cases. In these three cases, consulted institutions were described as based in countries of foreign investigators, but approval by local health authorities was granted as well. In other cases, the terms of engagement with community representatives, ahead of research activities, were seldom mentioned.[9]

The following observations are anecdotal, but are illustrative of the different weights put on ethical concerns during FHF outbreaks or their reporting. In one case only (Sanchez *et al.*, 2007), authors report that samples analyzed retrospectively were accurately anonymized ('In accordance with CDC institutional review board policies'). In three cases, material compensation was offered to study participants. There are at least five cases (Ksiazek *et al.*, 1999a; Villinger *et al.*, 1999; Baize *et al.*, 1999; Towner *et al.*, 2004; Hutchinson and Rollin, 2007) where no mention is made of participants' consent or oversight by an REC, while daily or iterative venipuncture was performed to generate research results. The report on the single intervention study (Mupapa *et al.*, 1999a) mentions how consent was sought, but there is no indication of any ethical review process.

Our review suggests that African REC were either not existing or not engaged at the time of outbreaks. A recent survey in the WHO African region (Kirigia *et al.*, 2005) has exposed the lack of REC in several countries. Moreover, in countries that did have an REC, a number of deficiencies in established processes were apparent, notably in the frequency of committees' meetings. Among countries where FHF outbreaks or cases have been detected in the past, the survey was able to collect information on REC existing in: Angola, DRC, Kenya and Zimbabwe. Gabon, Sudan, Ivory Coast and Uganda were among the non-responders. At the indicated time of the survey (2003), Congo did not have an REC but it had set up an ad hoc commission tasked with establishing proper committee foundations (Formenty *et al.*, 2005). Sudan has been part of a more recent external evaluation (Kass *et al.*, 2007) that emphasized recent progress and political will for capacity building of an ethics committee in this country.

Beyond Informed Consent and Ethics Review Processes: The Example of Benefit Sharing

Our review of the biomedical literature suggests that ethical issues have been infrequently and insufficiently addressed by field investigators during past outbreaks of FHF, and that they have mainly been limited to concerns over consent to participate. It is likely that a broader and richer range of ethical debates have taken place during such circumstances. We suspect that current methodological conventions and editorial stereotypes used in the biomedical literature do not leave much space for translating such a wealth of information into meaningful reports, beyond quantitative or binary data about informed consent and ethics review. Moreover, the same conventions give a one-sided perspective, the one seen from the investigators' angle. Missing so far are perspectives of affected communities in general, and of survivors in particular. One way to engage local communities in the debate would be through discussions over what benefits could be shared through the outputs of research activities carried out during FHF outbreaks. Until recently,

these activities have mostly supported the generation of descriptive epidemiological, virological or clinical data, with no or little immediate benefits for outbreak-affected communities. We should anticipate in a near future the production of specific therapeutic interventions such as antiviral agents, or post-exposure recombinant vaccine treatments (Feldmann *et al.*, 2007) with direct relevance to communities affected by outbreaks. The prospect for clinical trials to take place in the midst of FHF outbreaks is thus real and will need careful examination of a full range of ethical issues, including benefit sharing. With FHF, there are four essentially distinct categories of potential victims, including: (i) rural communities in sub-Saharan Africa exposed to the risk of infection through natural reservoirs or intermediate hosts; (ii) health care personnel exposed to the risk of sustained nosocomial transmission, typically in poorly equipped African hospitals; (iii) laboratory researchers accidentally exposed to virus samples and (iv) anticipated victims of bioterrorism acts. Potential beneficiaries of the results of clinical trials would thus differ in the nature and legitimacy of their concerns (real versus alleged), in the intensity of risk to which they are exposed (sporadic versus sustained), in their freedom of choice toward exposure and in their likelihood of access to future preventive or curative technologies. As a prerequisite to consultations over benefit sharing, the exact categories of beneficiaries of research on FHF should be explicitly named with utmost clarity when approaching communities genuinely affected by outbreaks. As shown by the recent controversy over the distribution of H5N1 virus specimens from Indonesia through WHO networks, a new dimension of inequities in shared benefits from outbreak investigations is being recognized. In this new debate, involved parties are no longer defined as affected communities versus communities at risk, both eventually sharing common exposures and interests. The polarization is now magnified toward poor countries urged to donate 'natural resources (clinical specimens, viruses and other microbes)' versus technologically advanced industrial countries with private interests (Sedyaningsih *et al.*, 2008). In this respect, the question of shared benefits resulting from outbreak investigations illustrates perfectly the global dimension of debates in public health ethics.

Duty to Care and Standard of Care: From Individual to Collective Definitions

With extremely high case fatality ratios, and a high degree of transmissibility in the absence of protective equipment, it is not surprising that outbreaks of FHF have seen a number of health care workers failing in their duty to care. In many healthcare settings of sub-Saharan Africa, where even everyday medical or nursing practices are not rewarded with access to appropriate working environments and decent livelihoods, the notion of duty to care becomes rather spurious for local health workers and attendance to FHF patients can amount to heroism. Several authors have argued that the duty to care is collective, rather than individual (Reid, 2005; Bensimon *et al.*, 2007; Dwyer and Tsai, 2008). For the case of SARS in Toronto, Bensimon *et al.* (2007) have proposed an ethical framework expanding the issue of duty to care from the individual to institutional and societal contexts. They conclude that the duty to care cannot be left simply to personal choice or an appeal to morality, but it implies additional protection from institutions and meaningful support from the society at large. This is an important point, which needs to be translated in the context of sub-Saharan Africa. To the extent that an outbreak of FHF has been recognized as a public health threat of international concern, this implies further commitment from the international community in providing institutional and societal safeguards to local volunteers. In addition, the international dimension of the outbreak response to FHF entails the exposure of foreign as well as local health care providers. Generally, experts mandated by international agencies to assist directly in patient care are outnumbered by epidemiologists, laboratory specialists and field researchers. This recurrent observation could simply reflect imbalances in the various profiles of available experts, in which case training additional clinicians remains an urgent priority. This might also reveal, on the part of collaborating institutions, a pattern of scientific priorities and interests rather distanced from direct patient care. If we admit as a normative principle that care has precedence over research, this pattern points to a collective breach in the duty to care.

Practically, thresholds of standard of care (including staffing ratios or sanitation standards, for example) could be defined, below which patient care should have absolute priority over the initiation of any research activity. Under current FHF circumstances, this would be a more appropriate and realistic definition of standard of care than definitions centered on individuals, such as the ones causing controversy about participants in clinical trials in developing countries (Lie *et al.*, 2004). Thresholds of collective standards of care would reflect the collective nature of outbreaks, and distribute equitably the benefits of intended research activities over the full community of victims, regardless of the fact that some of them (or possibly none) have given consent to be involved in

research. These minimal collective standards of care would also help define the limits beyond which additional activities offered by relief organizations could be considered as inducements for both individuals and communities to participate in research activities.

Current State of Affairs and Future Solutions

In the current absence of a universally endorsed code of conduct for outbreak investigations, what existing principles could legitimize the problematic ethical decisions faced by clinical investigators mandated by international organizations in response to epidemic emergencies? First, the boundaries between research and public health investigations in the context of FHF outbreaks need to be carefully defined on a case-by-case basis and in light of the existing national and international instruments. Useful guidance on categorizing projects as research or not has been elaborated by the HRPO in its interpretation of the Common Rule through the 'primary intent' principle. This is, however, based on a national legal principle, and it should be further examined at an international level as the possible ethical foundation for a more universal principle of interpretation and arbitration by coordinating authorities such as the WHO. However useful when one attempts to qualify activities as research or not, the 'primary intent' principle poses a number of problems, which we have acknowledged both as theoretical obstacles and as practical limitations in our qualifications of reviewed outbreak reports. In this article, we have also argued for ethical qualification to be complemented by the subsequent examination of additional criteria, such as the 'incremental risk' factor. The latter is based on judgment and needs to take into account the full complexity of events and circumstances, which define the particular vulnerability of FHF victims.

Second, the CIOMS 'International Ethical Guidelines for Epidemiological Studies' complement the Common Rule in defining conditions for waiving the principles of individual consent and ethical board review. The extent to which informed consent is required will depend on whether these studies are 'performed within the scope of regulatory authority . . . such as disease surveillance' or not. In order to define an adequate process for informed consent for research during FHF outbreaks, it is crucial that these points be clarified, in particular the exact meaning of 'disease surveillance' in this context. In our view, four options are possible. Studies requiring informed consent in the absence of other reasons to waive such consent can be defined as:

(1) any gathering of data for purposes other than direct benefit to this patient;
(2) any gathering of data for purposes other than direct benefit, or enabling better clinical management of other patients in this outbreak;
(3) any gathering of data for purposes other than direct benefit, better clinical management or better containment of the outbreak;
(4) any gathering of data for purposes other than direct benefit, better clinical management or better containment of naturally occurring outbreaks in endemic regions.

Such definitions, which encompass concentric circles, offer a clearer framework rather than the mere reference to 'disease surveillance', considering that the latter term carries semantic ambiguities that pertain to the scope of research activities (Calain, 2007). Furthermore, under the revised (2005) IHR, the scope of 'surveillance' activities has reached global dimensions. This implies that the boundaries between locally affected communities and globally threatened populations have vanished, as far as filoviruses or similar agents able to 'cause serious public health impact and to spread rapidly internationally' are concerned. In theory, this could lead to the disputable argument that, during FHF outbreaks any data collection contributing to useful generalizable knowledge would at the same time fall automatically within 'global' surveillance. There is thus a subtle shift in the definition of affected communities, moving the spectrum from local to global populations. This extension would create new ethical frameworks, if criteria such as 'disease surveillance' were to be used to waive some ethical safeguards. Outside of the framework of surveillance, it is clear that there are very few situations where waiving consent can be justified on the ground of emergency circumstances only, and recognizing these situations is particularly difficult. Evaluating whether or not 'it would be impracticable or prohibitively expensive' to obtain consent, for example, takes on a specific meaning in the context of a FHF outbreak response, which can be very different from considerations relevant for non-urgent use of biobank samples. The 'minimal risk' criterion (CIOMS, 2008) is problematic too: FHF patients' baseline risk is high, making even small incremental risks potentially highly significant. Evaluating the merit of such claims will thus be particularly difficult in such a context.

Community engagement could go some way to compensate these difficulties. However, while essential in itself, it is obviously not a substitute for genuine individual consent. Yet, the latter will remain problematic in most FHF outbreak situations. The posting of a 'Patient Care

Charter' (Epelboin *et al.*, 2008) inside isolation units and the systematic briefing of assigned foreign experts by coordinating bodies are possible innovations that could somewhat improve ethical standards during emergencies.

The more fundamental solutions, however, entail considerable upstream work along two directions: (i) the design of basic research protocols and standards prior to emergencies, and (ii) the establishment or strengthening of national and independent ethical research committees. These committees should have the capacity to review the adequacy of research protocols within proper cultural contexts, and with sufficient reactive capacity to respond in due time to emergencies. A further possibility could be: (iii) to involve potentially affected communities ahead of time, to obtain their feedback on aspects of the basic research design and thus gain valuable time in the community permission process during the outbreak itself. Beyond observational research, all three conditions are also important prerequisites to translate ongoing laboratory research into promising preventive or therapeutic interventions (Bausch *et al.*, 2008), and to seize future opportunities for at last decreasing substantially the dreadful fatality ratio caused by FHF. Such an approach, however, represents a public health paradigm shift, where outbreaks of FHF are no longer considered as single emergencies, but as recurrences of a more chronic problem requiring ongoing efforts.

Notes

1. We do not address specifically the equally relevant issues of isolation, quarantine, lax confidentiality and lack of privacy, except to say that they coincide to making FHF outbreaks unique challenges for field research.
2. See Bausch *et al.* (2008) for an updated list of known FHF outbreaks.
3. For an illustrative example of this diversity of actors, see WHO (2007b).
4. Following Kass *et al.* (2007), we consider 'institutional review board' (IRB) and 'research ethics committee' (REC) as synonymous denominations.
5. Quote: 'All network responses will proceed with full respect for ethical standards, human rights, national and local laws, cultural sensitivities and traditions'.
6. For example, WHO and technical partners have promoted a safe method for case confirmation and public health surveillance of FHF, using skin snips from deceased cases (Zaki *et al.*, 1999).
7. MeSH equations:
   (a) ('Hemorrhagic Fever, Ebola' [Mesh]) NOT ('The Journal of infectious diseases' [Jour]) (limited to humans)
   (b) ('Marburg Virus Disease' [Mesh]) NOT ('The Journal of infectious diseases' [Jour]) (limited to humans).
8. Blood sampling is defined here as blood taken by venipuncture (in addition or not to other samples).
9. An exception can be found in Busico *et al.* (1999).

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