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Toward a global foot and mouth disease vaccine bank network

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Summary

A network of foot and mouth (FMD) vaccine banks has been initiated with the support of vaccine bank managers and technical advisors that participated in a workshop held at the Institute for Animal Health, Pirbright, in the United Kingdom in April 2006. Terms of Reference that provide guidance for coordinated activities are under consultation. Practical and economic benefits can be realised from collaboration, which will be achieved through mutually acceptable mechanisms for the exchange of information and materials relevant to vaccine banks and their management. If administrative and technical hurdles can be overcome, the network has the potential to contribute significantly to the improved control of FMD worldwide. A 'global' and interactive vaccine bank association could be created by agreeing a system of resource sharing that could orchestrate additional emergency cover with vaccine or antigen from the reserves of network members.

Keywords

Foot and mouth disease – Vaccine bank managers – Vaccine bank network – Vaccines – Virtual bank.

Introduction

Work in the late 1970s, investigating the production of strategic reserves based on virulent foot and mouth disease (FMD) virus concentrates, eventually highlighted the advantages of using already inactivated bulk antigens (8). Subsequently, this led to several countries and groups of countries establishing FMD vaccine banks or reserves. These reserves are principally stored as concentrated and inactivated FMD virus antigen over liquid nitrogen for later formulation when required.

In 1982, the United States, Canada and Mexico signed a collaborative agreement establishing the North American FMD Vaccine Bank (1, personal communication). A joint FMD antigen bank known as the International Vaccine Bank was established in 1985 at the Institute for Animal Health (IAH), Pirbright, in the United Kingdom (UK), following an agreement between several European countries, Australia and New Zealand (NZ). The European Union (EU) Directorate General for Health and Consumers established the EU vaccine bank in 1992 and 26 countries have arrangements with this bank for the supply of vaccine or antigen, although a 2% decrease in the holdings has been reported since its inception (11). Six of these 26 countries are known to have their own national reserve as well (7), and many governments other than those in Europe have their own reserves under contracts with manufacturers; Argentina, for example, established its reserve in 2000. Though emergency banks were principally set up to combat inadvertent incursions of FMD (or other diseases) they have, in recent years, been given greater importance as a result of the perceived threat and possible consequences of a deliberate agro-terrorism action, as well as emerging vaccinate-to-live strategies for

FMD-free countries. Each of these managed reserves faces similar issues, such as strain selection and the manufacture, storage, formulation, testing and regulation of these vaccines, which they currently deal with independently. Therefore, practical and economic benefit could be realised through collaboration between those responsible for these vaccine banks or reserves. However, real and perceived issues of national security and the commercial sensitivities of manufacturers that supply banks have understandably led to confidentiality and restraint in regard to information exchange. Actual sharing of antigens in case of emergency need may be further complicated by a lack of common technical and regulatory standards between banks wishing to collaborate.

In most cases, FMD vaccine is made to order for a current and specific need, without surplus product, and provided ready formulated for use. This approach provides little flexibility to accommodate revisions to specification at short notice for emergency needs and prompted the establishment of vaccine/antigen banks. The EU vaccine bank has provided emergency vaccine to Albania and Macedonia (1996), Morocco and Algeria (1999), the Far East (2000), Turkey (2000 and 2006) (9, 10, 12) and more recently to Iraq (2009) in the face of increased incidence of FMD type A in the Middle East (6).

The World Organisation for Animal Health (OIE) convened an *ad hoc* meeting on antigen and vaccine banks for FMD in June 2004 at which the ability of banks to assist one another was discussed. This *ad hoc* group aspired 'to facilitate information exchange and harmonisation of methods and standards to assist countries in the establishment of vaccine banks, with special emphasis on FMD, including the development of a network of banks for exchange of information on cross-protection of vaccine antigens and to resolve issues relating to potential supply of antigens and vaccines between banks and regions'. It was recognised that even without shared access to antigens in an emergency, a vaccine/antigen bank network would have two main benefits:

– facilitating information exchange on matters such as the ability of banked vaccine strains to protect against current circulating FMD virus

– allowing exchange of materials and reagents such as trial blends of vaccine antigens and antisera.

Overall, such a network could provide both economic and logistical benefits, as follows:

– improvement and harmonisation of protocols

– avoidance of duplication

– reduction in the burden of stockpiling

– broadening of the range of available vaccine strains for all members of the network.

The *ad hoc* group met again in April 2005 to discuss, amongst other topics, the future development and operation of a potential vaccine bank network and the group noted the possibility for synergies with an EU funded FMD and classical swine fever (CSF) Coordination Action (CA) project initiated in January of the same year. This CA was designed to gather and share information relevant to the control of two of the most important viruses in the OIE list of notifiable diseases, FMD and CSF. The CA had developed a Work Package on vaccine reserves that had identified the need to develop a network of vaccine bank managers to facilitate the exchange of information and materials relevant to vaccine banks and their administration.

The purpose of this document is to provide an account of the concept and of the efforts towards making the network a reality and to encourage collaborations between FMD vaccine bank managers, owners, technical representatives, manufacturers and authorised parties.

Concept and benefits

Decisions about managing national or international reserves, and about what and how much should be held, are often considered in isolation, taking into account the global status of FMD and cost implications. In 2007, the minimum dose holding of vaccine strains in an emergency bank was considered and reported for Europe (5). In North America, simulation modelling of different scenarios is being used to estimate the number of doses required in the event of an outbreak (personal communication).

A coordinated approach to antigen/vaccine bank activities around the world through a network could aim to increase cooperative effort, mutual support and back-up for vaccine bank network members in order to improve international control of FMD by vaccination. Specifically, it could consider common vaccine bank issues such as vaccine dose requirements, virus strain selection, manufacture, formulation, testing and regulatory control, storage, security, maintenance, monitoring and disposal. This could lead to:

– sharing information and best practices

– avoiding duplication of effort, thus saving time, money and energy

– harmonisation of approaches and definition of standards where appropriate

– rationalisation and sharing of bank reagents

– identification of routes for independent testing and assessment of FMD antigens/vaccines

– monitoring of progress and technical developments relating to emergency FMD vaccines

– identification and promotion of areas of research that could lead to improvements in emergency FMD vaccine reserves

– increasing the efficiency of vaccine banks and the proficiency of vaccine bank staff

– offering expertise to member countries and to international disease control agencies such as the OIE and FAO to assist in the control of FMD by vaccination

– identification and removal of any constraints in the functioning of the network

– providing a unified voice in discussions with manufacturers

– investigations of how to share banked antigens, working towards a virtual international bank for FMD vaccines

– improvement in the availability of emergency vaccines and access to a wider range of vaccine strains and quantities.

Progress towards a network

Encouraged by the second *ad hoc* meeting on antigen and vaccine banks for foot and mouth disease, both a workshop and then a teleconference on key issues and concerns shared by antigen/vaccine bank technical advisors and managers took place under the auspices of the FMD and CSF CA.

The workshop was held at Pirbright in April 2006 and involved owners, technical advisors and managers of FMD vaccine banks from Europe, South Africa, Argentina, the Republic of Korea, Botswana, New Zealand, North America and Australia (see Fig. 1). This workshop discussed common concerns and experiences of managing such reserves, including current OIE regulations and guidelines for the establishment of vaccine banks; historical efforts towards the standardisation and harmonisation of practices and cooperation between European members; and the efforts within Work Package 4 of the CA in the gathering of information and coordination between vaccine bank managers (2).

The discussions led to the circulation of three documents. The first was a draft Memorandum of Understanding (MOU) for an International Network of Vaccine Banks for FMD Vaccine, following input from some of the participants. The second proposed the standards and protocols that should be followed by the banks. The third provided details of a methodology and format for regularly collating and reviewing data on antigen/vaccine quality using the key standards and protocols of the network.

A teleconference followed on the 15 May 2006 between representatives from the vaccine banks of Australia, NZ, the UK, the EU, Canada, the United States and Mexico, where, unanimous support was given to the creation of an international FMD vaccine bank network (3).

Many of the standards and protocols that it was suggested should be followed by the banks were directly taken from the OIE chapter on vaccine reserves that had been written following the 2004/5 OIE *ad hoc* meeting on FMD antigen and vaccine banks. The *ad hoc* group recognised that common standards would allow for assurance of quality

Fig. 1
Delegates that participated in the first meeting of the vaccine bank network at the Institute of Animal Health, Pirbright, United Kingdom, 4-5 April 2006
A report of this meeting is available at: www.foot-and-mouth.org/fmd-csf-ca/community/work-package-4-vaccine/D-WP4-2.pdf/view

and security of shared antigens as well as clear consistency of data on *in vivo* and *in vitro* stability, potency and strain differentiation. Overall, it was recognised that harmonised test procedures, common sources of antigens and assured high manufacturing standards would facilitate reagent/material exchange between network participants.

The *ad hoc* group unanimously supported a harmonised approach for reporting the above data and other information, such as research related to emergency antigens/vaccines, using a specific document template, largely thanks to the fact that many of the test approaches highlighted were already being used routinely by all the participants. Such data collection could also provide the basis for a summary that could be distributed within the network. The need for each network member to seek formal approval from its national authorities for information exchange was noted. It was widely recognised that such a reporting system would help to further establish the global picture for FMD and effectiveness of certain vaccine strains, as well as providing an up-to-date source of information on vaccine developments in the FMD field.

The need to create a secure web-based data repository for this network was seen as a key priority once agreement to the MOU had been reached. However, although there were no concerns raised over the content of the MOU, it became apparent that, aside from the length of time needed to identify appropriate signatories for this document, the draft MOU had different legal connotations in certain countries. Nonetheless, the principles of a network were established, including a Code of Practice for such an arrangement (see Appendix).

Key difficulties

Some vaccine banks do not divulge details of their contents (strains, doses, etc.) because they want to prevent this information from being obtained by anyone who might wish to deliberately introduce FMD virus into a country. However, the level of confidentiality that is maintained varies between vaccine banks. In some countries, the information is not published or otherwise made public, but is available to trusted government advisors and civil servants. It is conceivable, therefore, that a similar arrangement could be used on an international scale, whereby information could be shared within a small network of like-minded authorised persons subject to a confidentiality agreement. In contrast, other countries maintain much more stringent confidentiality and are currently unlikely to agree to share such information within this network. It is therefore proposed that initially, there would be no obligation to share information such as this. However, it must be recognised that this will considerably limit the value of the network and that the issue should be revisited once the network has established its final list of participants and its modus operandi.

It is important to maintain the momentum of this coordinated activity. A telephone conference held between the UK, Canada and NZ on the 27 November 2008 made it fundamentally clear that an MOU was a stumbling block to the progress of the network because of various political and legal issues in different countries, and that it should be replaced by a terms of reference (TOR) agreement. Draft networking arrangements taken from the current TOR are in the Appendix. Separate bilateral MOU documents may also have to be prepared for the sharing of reagents and other relevant materials. The various documents and guides that are required for such agreements must be ratified by several different groups of people in authority, and these people can be difficult to identify.

The way forward

Aside from the difficulty in agreeing upon TOR, undoubtedly the biggest hurdle to progressing this network is being able to approve a formal working mechanism to share information on the detailed holding stocks of the various strategic reserves without it being privy to potential terrorist groups. It is debateable whether the availability of information on the strains held in a vaccine bank would significantly increase the risks from bioterrorism. It would take considerable background knowledge of FMD to make use of this information and someone in possession of such knowledge could probably make a reasonable prediction already about which strains are likely to be held in vaccine banks. Moreover, there have been some notable *in vivo* studies recently, by Brehm *et al.* (4), confirming that if emergency vaccines are formulated at high antigen payload from strategic reserves, they have a wide coverage against heterologous strains of a given serotype, making selection of a 'candidate terrorism' strain that would not be covered by vaccine reserves quite difficult. Nevertheless, there is clearly variability in the level of confidentiality between different vaccine banks and differences in the extent to which information is disseminated. It is necessary, therefore, to develop a method which accommodates these different levels of confidentiality and at the same time allows restricted accessibility and sharing of such information within a small network of like-minded authorised persons. Some countries/organisations will not agree to share much of the information at their disposal and therefore the interested parties should, in the first instance, agree to progress the concept and then, at a later date, decide how, and at what level, an exchange in information can occur that is acceptable to all those who wish to participate. Whilst certain members may be willing to disseminate more

information than others it would be hoped that in the longer term confidence would increase and the value of belonging to such a community would further open the dialogue between the different banks. The work by Brehm *et al.* (4) for serotype A might be extended through collaboration within a vaccine bank network. This could lead to a situation in which banks need only stockpile a few select vaccine strains, which has obvious financial benefits, and therefore the importance of studying this further with other vaccine serotypes cannot be overstated. This could be coordinated and tasked through a network of banks, each of which could examine a specific vaccine strain *in vivo*, thereby sharing the research cost burden and establishing both an effective and cost-efficient depository.

In the coming months, key negotiations will take place between interested parties from around the world to find a way through these difficulties. It is likely that the network would require a closed structure in which specific information relating to the use of banked vaccines could be shared within a very limited group of government advisors, civil servants, scientists and vaccine manufacturers. Although the TOR suggest more than this, the network might start by exchanging some basic data, perhaps within a core group. Other data, as explained in 1.1 in the Code of Practice (see Appendix), could in time increase the collective knowledge and be available to an expanded (but closed) group. By its very nature the group would be dynamic and a neutral secretariat could provide the required stability.

Clearly, it will be some time before these documents will be ratified and have all the necessary signatories, but additional financial support would be welcomed, possibly from a new EU collaborative project, to continue the good work that has already been done and to develop this goal further. This will provide an endorsement of the network, and its infrastructure and support its secure web-based reporting system to allow the exchange of information or reagents, which will undoubtedly be a valuable step toward efficient control of FMD outbreaks.

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Vers la mise en place d'un réseau mondial de banques de vaccins contre la fièvre aphteuse

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Résumé

Un réseau de banques de vaccins contre la fièvre aphteuse a démarré ses activités grâce au soutien de responsables de banques de vaccins et de consultants techniques qui avaient participé en avril 2006 à un atelier tenu à l'Institut pour la Santé animale (laboratoire de Pirbright) du Royaume-Uni. Une réflexion est menée actuellement sur le mandat du réseau, visant à encadrer ses futures activités de collaboration. La collaboration offre des avantages aussi bien pratiques qu'économiques à travers les mécanismes mis en œuvre pour partager les informations et les matériels pertinents pour le fonctionnement et la gestion des banques de vaccins. Une fois surmontés les obstacles administratifs et techniques, le réseau sera en mesure d'apporter une contribution importante à l'amélioration de la lutte contre la fièvre aphteuse dans le monde. Une association mondiale et interactive de banques de vaccins pourrait ainsi être créée, axée sur un système de partage de ressources capable d'orchestrer une couverture vaccinale d'urgence en utilisant les stocks de vaccins ou d'antigènes détenus par les membres du réseau.

Mots-clés

Banque virtuelle – Directeur de banques de vaccins – Fièvre aphteuse – Réseau de banques de vaccins – Vaccin.

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Hacia una red mundial de bancos de vacunas contra la fiebre aftosa

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Resumen

Los autores describen una red de bancos de vacunas contra la fiebre aftosa iniciada con el apoyo de los administradores de bancos de vacunas y asesores técnicos que participaron en un taller celebrado en el Instituto de Sanidad Animal (Pirbright, Reino Unido) en abril de 2006. Ahora mismo está en fase de consulta el mandato en el que ha de encuadrarse la realización de actividades concertadas. La colaboración, concretada en mecanismos mutuamente aceptables para intercambiar información y material de interés para los bancos de vacunas y su gestión, puede deparar tanto resultados prácticos como beneficios económicos. En potencia, y suponiendo que se logren superar los obstáculos administrativos y técnicos, la red puede resultar de gran utilidad para mejorar la lucha mundial contra la fiebre aftosa. Consensuando un sistema de utilización mancomunada de recursos, cabría la posibilidad de establecer una asociación 'mundial' e interactiva de bancos de vacunas que en situaciones de emergencia ofreciera un mayor nivel de cobertura, con vacunas y antígenos de las reservas de los bancos integrantes de la red.

Palabras clave

Administradores de bancos de vacunas – Banco virtual – Fiebre aftosa – Red de bancos de vacunas – Vacunas.

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Appendix

Draft networking arrangements

The network has no budget and will act through its members, each of whom will be financially independent and supported by their own resources.

The network should

1. Meet at least annually to appoint a secretariat, review progress, identify priorities and agree plans for the network.

2. Produce an annual network report through the secretariat for the members and their authorities.

3. Operate initially for a limited period of between 3-5 years, with a review of the value of continued interaction thereafter.

4. Agree a TOR (terms of reference) to identify objectives and strategic activities as well as to facilitate the exchange of materials and information.

5. Develop processes based on best practice to achieve equivalence in FMD vaccine bank standards. In this regard, the network will aim to hold and use antigens/vaccines produced in compliance with OIE recommendations and will evaluate the applicability of guidelines from the EU Committee on Veterinary Medicinal Products.

6. Concertedly address, by application of risk analyses, the appropriateness of types and the optimal amounts of antigens/vaccines required in reserves.

7. Promote the development of *in vitro* tests that provide improved correlation with protection against challenge and ultimately reduce reliance on animal testing.

8. Consider practical uses of emergency antigens/vaccines no longer required in banks or that have or are about to have exceeded their holding period.

9. Identify research requirements and where appropriate develop joint research projects.

10. Develop guidelines for successful implementation of emergency vaccination.

11. Develop or access web-based tools for the network to share and make available laboratory information such as vaccine strain matching results, as close to real time as possible.

12. Maintain a database of FMD vaccine bank managers and their field of expertise.

Coordination

A secretariat will be required to organise the annual meeting and compile and disseminate minutes and reports, to maintain a secure web-based facility that has already been established (http://www.foot-and-mouth.org/fmd-vaccine-banks) and to facilitate the implementation of the agreed plan of work. The secretariat will be provided by one of the network representatives to coordinate network activities. The decision on who will act in the capacity of the secretariat and for what period of time will be taken at the network meetings.

It is realised that to facilitate the sharing of information and materials the Network will require a secure and confidential system. This might be achieved electronically through a web-based facility providing that it assured secure data input of offered antigens and other reagents/materials. Requests for such resources could be made via an independent bank administrator who would be the initial liaison between the provider and the consumer. Thereafter, bilateral arrangements would secure emergency access to the particular requirement. In this way banked vaccines would be available to all members without disclosure of the entire contents of the bank.

Code of practice

In order to realise the above objectives and strategic actions, the participating members have developed the following code of practice for exchange of information and materials between originators and recipients within the network.

1. Exchange of information

1.1. This includes, but is not limited to, methods of analysis to decide on optimal quantities and types of vaccine, methods of selecting vaccine strains, infrastructure required to support an efficient vaccination campaign, recommendations for improving vaccine efficacy, methods for increasing shelf-life of antigens/vaccines including assessment on the long-term stability of antigens under ultra low temperature storage, improvements to potency testing and alternatives to challenge, development of alternative methods to detect infected animals following vaccination, methods for post-vaccination serosurveillance and means of safe disposal for vaccines.

1.2. The annual report of the network and the minutes of its meetings should be agreed by all the participants prior to finalisation. A decision will be needed on whether these documents (in whole or part) can be disclosed more widely and such disclosure shall require the agreement of all of the participants.

1.3. Information may be passed from originator to recipient verbally or in writing. Information produced by one vaccine/antigen bank remains the

intellectual property of that bank until such time as it is released by the originator into public access by publication in print or via the internet. Until then, it may be utilised by other vaccine/antigen banks in the network upon request or via a shared access website, provided that any publications that arise from using the information are agreed by the originator, including appropriate acknowledgement of, or co-authorship with, the originator. Whilst the information remains the intellectual property of the originator, it shall not be passed on to third parties by the recipient without the express consent of the originator.

2. Exchange of materials

Such an exchange of materials will principally involve small-scale vaccines/antigens or anti-serum representing vaccine strains held in strategic reserves. FMD vaccines or inactivated FMD virus antigen held by one vaccine/antigen bank may be passed to another vaccine/antigen bank if there is a requirement for either independent testing, confirmatory testing, or for experimental analyses or the production of reference materials such as bovine vaccinal sera for improved vaccine strain selection.

Equally, antisera derived from animals that have been immunised with vaccines that are representative of a component of an antigen reserve, and that either have, or have not, been subjected to challenge/protection testing can be used by a network. Such reagents can be used for serological assessment of the suitability of vaccine strains for use to control particular field isolates or for input into other research studies such as the statistical validation of alternative routes for *in vitro* potency estimation. In addition, antisera may also be passed to another vaccine/antigen bank if there is a requirement for either independent testing, confirmatory testing, or for other experimental analyses.

Such an exchange of materials may come within the remit of a collaborative research project, or arise because such experiments cannot be completed by the originator themselves.

In such cases, the recipient shall agree not to pass the material on to any third party, nor to exploit it commercially without the express written consent of the originator. Furthermore, the recipient will provide the originator with the results of all the testing and/or experiments carried out using such materials or the reference materials derived from them including any novel analysis that is undertaken. The recipient may utilise the results of their own studies using the originator's material without the originator's consent, except in the context of refereed publications resulting from such analysis which must be agreed with the originator and with appropriate acknowledgement of, or co-authorship with, the originator. Presentations or reports made by the recipient that utilise the results of any analysis of the originator's material, should also acknowledge the originator as the source of the material.

3. Shared access to antigens and vaccines for more comprehensive global cover

Whilst a prerequisite to any antigen bank or vaccine reserve is to have the most comprehensive stock-pile of vaccine strains available that are pertinent to any given outbreak situation, realistically this is neither logistically nor economically plausible. Therefore, antigen/vaccine reserves are established on the basis of the likeliest perceived risk and on the minimum amounts of each vaccine strain that should be stockpiled. Thus, antigens/vaccines are obtained/incorporated into antigen/vaccine reserves on a prioritised basis. However, there is recognition that

FMD is a global disease with a global risk of incursion that could occur from any source such that there may well be instances where a national, or international reserve, does not have any, or enough, of the most appropriate vaccine strain to assist in control of a particular disease incursion. This could be counteracted by an agreed access to supplies from other antigen reserves which hold a more relevant vaccine strain. In part, this is already addressed by some national authorities who hold their own reserves but also have access to the European Union antigen bank.

In order to maintain confidentiality of the stockpiles held by any given bank within the network, any request by another network member for supply of a specific vaccine antigen could be made through a single key contact, such as the network secretariat, who on the requestor's behalf will seek potential supply from any other member of the network. Should another network member be willing to support such a request then, in the first instance, this will be mediated through the key contact to the requestor. However, since the issue of confidentiality is principally based over bioterrorism, its value is only in respect of the vaccine strains that are not held by the reserves and is thus amenable to bilateral communication between both requestor and supplier over the final arrangements for access.

Under such arrangements, the requestor shall bear the full costs of the formulation, bottling, shipment and replacement of this antigen stock, including any necessary testing, on implementation and shall agree not to pass the vaccine on to any third party, nor to exploit it commercially without the express consent of the supplier. Furthermore, the requestor will provide the supplier with any results if it is subsequently used for control purposes in the field and following thereafter any serological surveillance that is undertaken.

The requestor may not utilise the results following implementation of an immunisation campaign using vaccine provided by the supplier without the supplier's consent, including the context of refereed publications resulting from such analysis which must be agreed with the supplier and with appropriate acknowledgement of, or co-authorship with, the supplier. Presentations or reports made by the requestor that utilise the results of any analysis of the supplier's vaccine, should only acknowledge the source of the material with the express permission of the supplier.

4. General provisions

Use of biological samples and reagents by the recipient should be limited to the specific purpose for which they were submitted/requested, unless additional written authorisation is obtained.

The biological materials supplied by a vaccine/antigen bank may have characteristics which are unknown or difficult to determine and which may pose potential hazards and risks during their handling, delivery, use, disposal and overall treatment and possession. The recipient(s) hereby assumes all liability with respect to any risk arising from these materials and in no event shall the originator be liable to the recipient(s) or third parties for claims arising there from, even in the event of negligence. It is the responsibility of the recipient to get authorisation from their national authority to be able to import biological materials.

Additional constraints on the use by recipient(s) of materials and information provided by the originator may be imposed by third parties that have given the materials or information to the originator in the first place.