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In the course of my work, I unexpectedly discovered some areas that had not been seriously discussed yet...
Frank Burnet

African swine fever: one hundred years later

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SUMMARY
This brief report pays tribute to Robert Eustace Montgomery (1880–1932) whose name is associated with the discovery of African swine fever (ASF). A hundred years ago, he published a major report on study of new highly dangerous disease carried out in 1900–1917 in the East Africa. The infection fundamentals have been established and described – the etiological, immunological and nosological uniqueness of the infection, fatal susceptibility of domestic pigs, clinical sings and pathomorphology, viral etiology, natural reservoir and source of the infection, survival of the virus outside the body, many specific epizootological aspects. Taking into account current high publication activity it has been concluded that there is a large body of multi-faceted research focused on African swine fever. Gap analysis carried out by the large team of the European researchers and experts revealed the most challenging aspects – wild boars, ASF survival and transmission, biosecurity and surveillance. In addition to the gaps mentioned in these conclusions and recommendations there are serious gaps in African swine fever immunology, namely in protective immunity mechanisms, virus-macrophage interaction, *in vitro* virus phenotypic signs correlating with its virulence, etc. Evidently, it is hardly possible to expect development of anti-ASF vaccines and particularly the vaccines capable of preventing and effectively protecting against ASF epizooty according to the general understanding without addressing these issues.

Keywords: review, R. Eu. Montgomery, African swine fever, current panzooty, Gap analysis

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Африканская чума свиней через сто лет

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РЕЗЮМЕ
В кратком сообщении воздается должное Роберту Юстасу Монтгомери (1880–1932), с именем которого связано открытие африканской чумы свиней. Сто лет назад им опубликован масштабный отчет об исследованиях этого нового особо опасного заболевания, проведенных в 1900–1917 гг. в Восточной Африке. Установлены и описаны основополагающие положения – этиологическая, иммунологическая и нозологическая самостоятельность данной инфекции, фатальная восприимчивость домашних свиней, клиника и патоморфология, вирусная этиология, природный резервуар и источник заражения, устойчивость вируса вне организма, многие частные элементы эпизоотологии. Применительно к текущей ситуации на основании высокой публикационной активности сделано заключение о чрезвычайном массиве разносторонних исследований по африканской чуме свиней. GAP-анализ (анализ пробелов, Gap analysis), выполненный большим коллективом европейских ученых и специалистов, позволил определить наиболее проблемные вопросы: дикие кабаны, выживание после африканской чумы свиней и трансмиссия, биобезопасность и надзор. Помимо отмеченных в этих выводах и рекомендациях, серьезные пробелы существуют в иммунологии африканской чумы свиней, в частности, относительно механизмов протективного иммунитета, взаимодействия вирус – макрофаг, фенотипических признаков вируса *in vitro*, коррелирующих с вирулентностью, и другие. Очевидно, что без решения этих вопросов вряд ли возможно рассчитывать на получение вакцин против африканской чумы свиней и особенно на их профилактическую и противоэпизоотическую эффективность в общепринятом понимании.

Ключевые слова: обзор, Р. Ю. Монтгомери, африканская чума свиней, текущая пандемия, GAP-анализ

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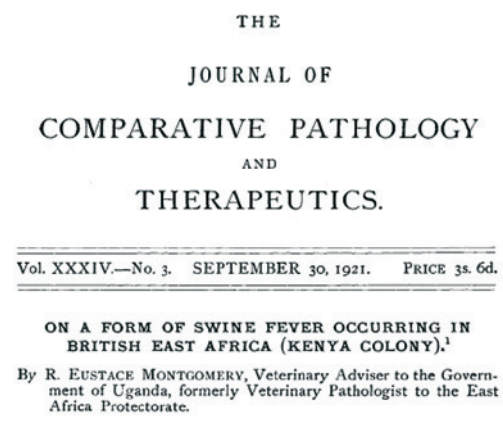
One hundred years ago Robert Eustace Montgomery (1880–1932) – distinguished veterinarian and pathologist, researcher of exotic diseases of the period of the first discoveries (Photo 1) – published results of the large-scale observations and experiments on African swine fever (Photo 2).

According to the Biographical Database of Southern African Science [1], R. Montgomery graduated at the Royal (Dick) Veterinary College in Edinburgh, Scotland, in 1903. After special duty in India and Canada, in 1907 he was sent by the Liverpool School of Tropical Medicine to investigate sleeping diseases (zoonosis, serious disease of humans and domestic animals) in Central Africa. The results of his investigation were presented in several papers published in the *Annals of Tropical Medicine* (1908–1909). In 1909 he was appointed as a pathologist to the East African Protectorate and in the same year participated to the Pan-African Veterinary Congress held in Pretoria on occasion of official opening of the Veterinary Research Institute in Onderstepoort, where he presented a report on "Trypanosomes and their transmission (Fly Disease) in relation to South Africa", published later in the *Proceeding of the Rhodesia Scientific Association*. He visited South Africa again in 1912 in connection with cattle immunization against East Coast fever. During the First World War (1914–1918) he served with the rank of Major in the East African Veterinary Corps. In 1917, R. Montgomery started the Veterinary Institute at Kabete (Kenya) and in 1918 he was appointed Director of Veterinary Research for the Union of South Africa. In 1920–1921, he was the first President of the South-African Veterinary Medical Association. From 1923 to 1926 R. Montgomery was a veterinary adviser to the governments of Kenya, Uganda, Tanganyika, and from 1930 – to the Colonial Office.

A truly fundamental R. Montgomery's contribution to veterinary science and practice is associated with the discovery of African swine fever (ASF) and the generalization of multi-year investigations of this newly discovered disease and some related phenomena, such as epizootology of exotic infections of wild animals, their role as reservoir, endemicity, that were non-trivial for the early XXth century. Current situation demonstrates that his contribution is truly epochal[1]. Detailed final report on the studies of African swine fever at the Nairobi Veterinary Laboratory (Kenya) started in 1900 was compiled by him in 1917 but it was published only four years later due to external reasons (war, change of jobs) [1, 3, 4].

[1] The second name of ASF is a *Montgomery disease* in the honor of R. Montgomery.

Photo 1. R. Eu. Montgomery [1]



THE

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ON A FORM OF SWINE FEVER OCCURRING IN BRITISH EAST AFRICA (KENYA COLONY).[1]

By R. EUSTACE MONTGOMERY, Veterinary Adviser to the Government of Uganda, formerly Veterinary Pathologist to the East Africa Protectorate.

Photo 2. Reprint of the historical publication on African swine fever [2]

In a large two-part paper [3], R. Montgomery gave the first description of signs of an unknown disease that emerged during the first attempts of rearing of pigs of European breeds imported from the metropolises by white settlers for home consumption or pork production. Cases of the disease, very similar to classical swine fever (CSF) well known in Europe, were officially registered on several farms in British East Africa but supposedly had a broader, epizootic, distribution.

Natural and experimental infection clinical picture and pathomorphology were described, infection natural reservoir and source (persistently and asymptomatically infected local warthogs – *Phacochoerus africanus*) were identified as well as the infectious agent was found to survive outside the animal body and in animal carcasses for a long time. Domestic pigs appeared to be fatally susceptible to parenteral infection with warthog blood but the infection was not transmitted by contact or by air that was interpreted as indicative of animal reservoir resistance and even then of low ASF contagiousness[2].

Experiments on cross-infection of CSF-immune pigs and passive protection from the infection with anti-CSF immune serum effectively and widely used for simultaneous vaccine-serum inoculations in pig industry at that time showed that the disease under study was new. Sera from wild pigs were also ineffective, i.e. fundamental fact of the lack of humoral protection against ASF became known even then. Attempted immunization with the heat-inactivated infectious material had no effect.

New infection was finally defined as an independent nosological form named as *East-African swine fever* in 1910. Further characterization of ASF, its causative virus, main principles of immunology and epizootology up to modern studies has improved the basic knowledge on the disease confirming the postulates laid down in the outstanding R. Montgomery paper [1, 3, 4].

In this context, current panzootia and resulting known stalemate undoubtedly require extraordinary solutions. Based on analysis of the data from PubMed[3] [5], worldwide ASF-associated publication activity highly intensified in recent years (Fig. 1) reflects both great scientific interest and scope of research activities.

A lot of international institutions and specially established associations with the World Organisation for Animal Health (WOAH) and Food and Agriculture Organization of the United Nations (FAO) as major players are involved in this common work. It should be noted that the following systems and organization are also highly engaged in the said activities: EMPRES (Emergency Prevention System for transboundary animal and plant pests and diseases, FAO), GF-TADs (Global Framework for the Progressive Control of Transboundary Animal Diseases, FAO), GARA (Global African Swine Fever Research Alliance, USA), Stop ASF (Public and private partnership programme, FAO/OIE), EFSA (European Food Safety Agency, EU), VACDIVA (EU Horizon 2020 Project on development of effective vaccine against ASF). Each organization combines and coordinates the research activities of several dozen up to more than one hundred and fifty participants (laboratories and institutions). The research effectiveness is discussed and evaluated in detail followed by development of agreed conclusions and solutions at regular scientific events and webinars[4]. Research outcomes are presented in a wide range of publications.

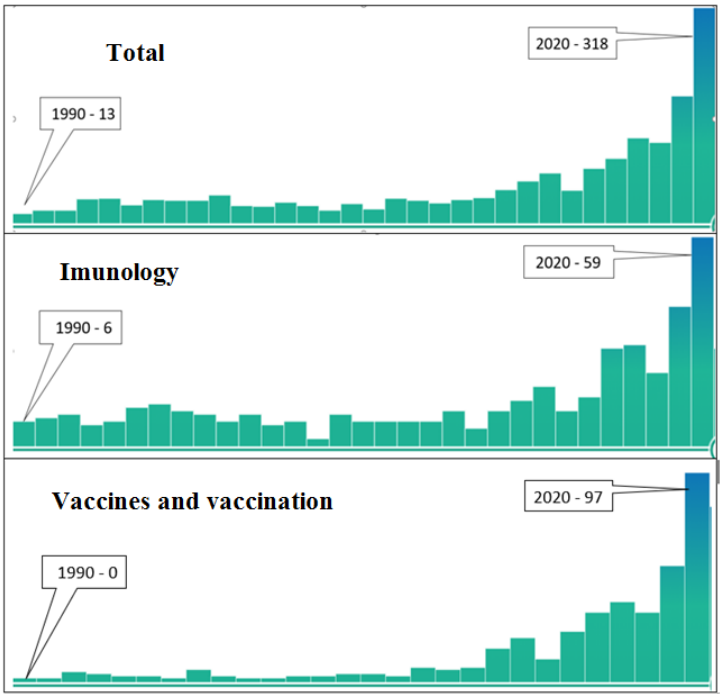

Fig. 1. Thirty-year dynamics of annual full-text publications on key ASF aspects (in call-outs) [5]

The EFSA Panel On Animal Health and Welfare (AHAW) activities and extended reporting and analytical publications in the *EFSA Journal* (for example, [6]) are of particular interest.

In particular, significant results were obtained during the Gap analysis[5] of management of short-term ASF risks for the disease control recently performed by a large team of reputable scientists and specialists in view of the aggravating disease situation in the participating European countries and published in the abovementioned periodical [5]. The timeliness of the said Gap analysis is obviously justified by rapidly increasing spontaneous large body of unsystematic publications that are still not associated with any significant anti-epizootic effectiveness.

Since the Gap analysis methodology is based on expert opinion of the persons whose interests are in any way related to the addressed task, respondents of the widest stakeholder range from pig farmers, hunters, veterinarians up to officers at high managerial level and all relevant officials and private professionals engaged in ASF control – national Veterinary Services and Ministries of Agriculture, European Veterinary Association, farmer's organizations, hunters' organizations, agribusiness, environment protection and management organizations, etc., taking into account different epizootogical status of the represented territories (first infected or endemic,

[2] This question is still debated. According to modern concepts, this type of pathogen-host relationship is defined as *persistent tolerant infection*.

[3] PubMed® is the largest data base of medicinal and biological publications at the US National Library of Medicine maintained by the National Centre for Biotechnology Information (USA), it contains more than 33 million citations of scientific literature (journals, books, other publications) [5].

[4] For example, recent public VACDIVA workshop (First International Workshop for the Pig Sector, October 1, 2021).

[5] Gap analysis is a method (or process) of the strategic analysis that compares actual result with what was expected for the identification of the challenging areas – suboptimal or missing strategies, structures, capabilities, processes, practices, technologies, skills, and recommends tools for the situation improvement and for meeting the goals. Unlike risk assessment focused on the future, the object of Gap analysis is the current state [7]. It is well known that recently Gap analysis has been actively used by the WOAH to improve the national veterinary service performance (PVS Pathway).

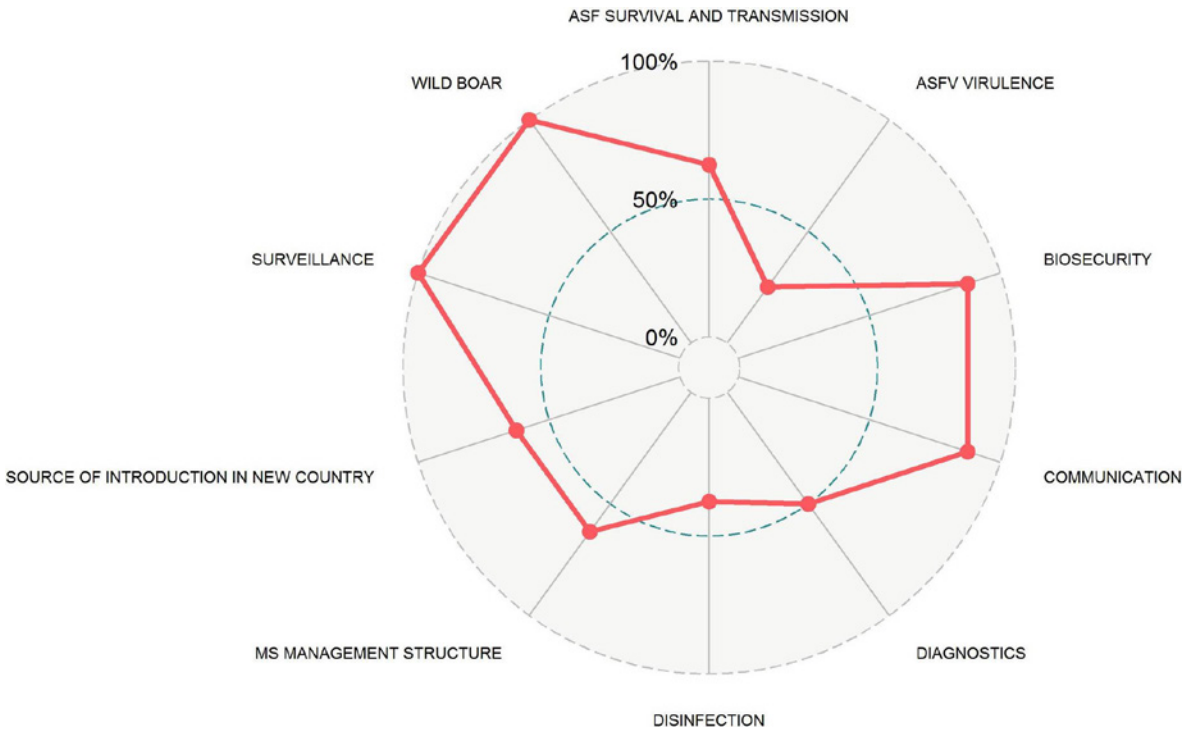

Fig. 2. Prioritization of currently important aspects identified by the Gap analysis, in percentage [6]

at infection risk, infection free) were involved to ensure its objectivity.

For an expert assessment of relevance based on a total analysis of the results published around the world, a number of "hot" issues covering the most currently important relevant scientific and practical areas in the context of an uncontrolled aggravation of the situation primarily in Europe were formulated. In particular, they included (*i*) role of survived animals in further ASF spread, (*ii*) virus virulence and possibility for live vaccine development, (*iii*) biosecurity in the broad sense of controlling infection spread risks, (*iv*) intersectoral communications for maximum coordination of all stakeholders' actions, information sharing, training, (*v*) sensitivity of diagnostic tests, non-invasive methods for wild boar, (*vi*) disinfection of various objects, destruction of wild boar carcasses, (*vii*) contribution of governmental bodies to international cooperation and funding, (*viii*) role of import, migration, pathways, objects in the infection introduction to the infection-free countries, (*ix*) passive surveillance in wildlife, border control, zoning for trading, early infection detection, (*x*) ecology, epizootology, control of wild boar populations. The Gap analysis results were summarized and presented in the form of spider graph (Fig. 2).

The conclusions and recommendations arising from this prioritization indicate the main point: the most popular trivial and conventional directions in modern ASF research, such as diagnostics (availability of faultless polymerase chain reaction), disinfection (everything was done a long ago), are not currently significant, and numerous publications (see Fig. 1) show that the main gap associated with the virus virulence studies (endless genotyping) is the unsuitability of the proposed attenuated virus variants as vaccines, according to generally accepted immunology and protectivity concepts. The main challenging gaps requiring primary attention were identified in four out of ten categories.

The crucial gaps in relation to *wild boar* were both organizational ones – necessity of harmonized wild boar population density estimation and ASF reporting in the wild, determination of the methods for reducing the absolute number of wild boar – and scientific ones – elucidation of the mechanisms for ASF spread and ASF virus persistence in the wild, possibility and importance of direct-contact infection transmission in wild boar taking into account their behavior.

In relation to *ASF survival and transmission*, it was shown that process management requires better knowledge and understanding of the insect vector role in biological and mechanical transmission of the infection, role of contaminated abiotic environmental factors and feed, potential risks associated with production, processing, transportation, storage of forage materials, different beddings, household items, porcine products and with personnel.

In relation to *biosecurity*, the important identified gaps were as follows: lack of effective measures for prevention of transboundary ASF introduction in the regions and holdings with different husbandry systems, for prevention of the infection transmission between wild boar and domestic pigs as well as potential risks of backyard farm involvement. Other gaps were considered serious: low public awareness of ASF, and the fact that social and economic situation, rural community lifestyle, as well as traditional agricultural practices were not appropriately taken into account.

The following was considered of high priority for the *surveillance* aimed at mitigation of risks of ASF introduction to the disease-free countries/regions: enhancement of border control of people, transportation vehicle, commodity movements, passive surveillance for and early detection of

dead animals (primarily, wild boar), methods for the agent detection (forage materials, items after decontamination), sensitive and rapid pen-side diagnostic kits to be used in the field, non-invasive tests for wild boar [6].

A common disadvantage of the said Gap analysis is, of course, the absence of the questions on ASF immunology addressed to the well-known numerous gaps in the questionnaire, while all efforts are focused on identification of virulence genes for their removal and virus attenuation. According to the recent publications with the participation of J. M. Sánchez-Vizcaíno [8], despite of a wide information flow, knowledge about immune defense mechanisms is very scarce. Such topic segregation can be attributed for the peculiar local interests of the Western European community in the current context.

However, in another comprehensive Gap analysis with a similar set of questions carried out on the GARA initiative (USA) [2], immunity-associated challenges were also not adequately addressed. The following clearly chronic gaps remain beyond the routine research: virus interaction with macrophages and, in general, a role of these unique cells in pathogenesis and immunity, virus-induced intracellular processes and virus reproduction, hemadsorption as antigenic modulation of host cell, hemadsorption antigen, serotyping hemadsorption-inhibition test, other *in vitro* phenotypic close-to-reality signs correlating to virulence and immunity, namely, intrapopulation virus heterogeneity, lack of protective humoral response of the immunity system (trivial virus neutralization), culture models for direct *in vitro* testing of protective antigen expression and phenomenology of cellular and intercellular protective reactions (interactions of antibodies with virus particles, $CD8^+$ T-lymphocytes-killers and other cytotoxic effectors with infected target cells, immune cytolysis morphology), effector potential of T-cell-mediated immunity.

It is hardly possible to expect development of anti-ASF vaccines and particularly vaccines capable of preventing and effectively protecting against ASF epizooty according to general understanding without addressing these issues, especially without determination and comprehensive characterization of the immune response effector phase using modern research methods, focusing only on acquired resistance to challenge (i.e. at the animal level). At the same time, the answers to many of the above questions were obtained earlier during the research carried out by the Biochemistry and Immunology Laboratories of the Federal Research Centre for Virology and Microbiology (Pokrov, Russia) and widely covered in the national scientific literature [9, 10].

It is noteworthy that the American Gap analysis, probably for the first time in relation to ASF panzootia control, raises the question about the reasonability of total destruction of suspected susceptible population including emergency slaughter of tens of thousands of pigs that results in significant financial losses, provokes all forms of owners' resistance and is ethically challengeable. Hence, alternative solutions to this socio-economic problem addressing the general public requirements without prejudice to effectiveness of anti-epizootic measures are required [2].

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