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HUMAN AND ANIMAL VACCINE CONTAMINATIONS

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ABSTRACT

Vaccination is one of the most important public health accomplishments. However, since vaccine preparation involves the use of materials of biological origin, vaccines are subject to contamination by micro-organisms. In fact, vaccine contamination has occurred; a historical example of vaccine contamination, for example, can be found in the early days of development of the smallpox vaccine. The introduction of new techniques of vaccine virus production on cell cultures has lead to safer vaccines, but has not completely removed the risk of virus contamination. There are several examples of vaccine contamination, for example, contamination of human vaccines against poliomyelitis by SV40 virus from the use of monkey primary renal cells. Several veterinary vaccines have been contaminated by pestiviruses from foetal calf serum.
These incidents have lead industry to change certain practices and regulatory authorities to developmore stringent and detailed requirements. But the increasing number of target species for vaccines, the diversity of the origin of biological materials and the extremely high number of known and unknown viruses and their constant evolution represent a challenge to vaccine producers and regulatory authorities.

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Introduction

Vaccination is without doubt the most cost-effective means of preventing, controlling and even eradicating infectious diseases. One shortcoming of this strategy, however, is linked to the use of biological material of animal or human origin for the production of vaccines. Contamination can occur at various stages of vaccine preparation, resulting from the accidental introduction of undesirable extraneous agents present in raw materials or introduced during the production process. Vaccines can also be 'contaminated' by the reversion to virulence of attenuated viruses used as active ingredients, or further to residual pathogenicity resulting from incomplete or defective inactivation. Throughout the years, there have been several episodes of contamination of human and veterinary vaccines, leading industry to change certain practices and regulatory authorities to develop more stringent and detailed requirements. Assuring viral safety of vaccines poses a real challenge to manufacturers and regulators because of the increasing number of target species for vaccines, the diversity of the origins of biological materials and the extremely high number of known and unknown viruses that can potentially contaminate vaccines.

The known and the unknown: the biodiversity of animal species

Vaccines are used to prevent infectious diseases in humans and various animal species (including mammals, birds and fish). A total of more than 62 000 vertebrate species have been recorded, including almost 9000 bird species, around 5500 mammalian species and 31 500 fish species - only a few of these are targets for vaccines. It is estimated that 99% of mammalian species have been identified. With modern molecular technology, species can be differentiated according to their genotypes with increasingly detailed comparisons of species limits and evolutionary relationships (taxonomic revision). There are 2277 rodent species, belonging to 481 genera, accounting for 42% of recognized mammalian species, and over 1100 species of chiroptera (bats), that may be sources of new emerging infections. A great effort is being made to reduce the use of animals in biomedical research, testing and production, both for ethical and safety reasons. Historically, the production of viral vaccines has required the use of animals, but they have increasingly been replaced by cultured cells derived from various animal species. The number of potential cell substrates is extremely large. With the development of new veterinary and human vaccines, new mammalian and insect cell substrates have been developed. Excluding the presence of adventitious agents from these cells can also be problematic, however, particularly for cells derived from species for which virological investigation has been limited.

The known and the unknown: the biodiversity of bacteria and viruses

Regulatory authorities request testing for the presence of viruses in starting materials as well as in finished products, and have established lists of extraneous agents to be tested in medicinal products and immunologicals. But these lists are probably not comprehensive, and should be revised as technology and the overall global situation evolve. Furthermore, the possibility of

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unknown agents must be taken into consideration; it may be possible to detect an extraneous agent only if one is searching for it. Nowadays the estimated number of known bacterial species is roughly 5000, but the real number could exceed 50 000, thus making the percentage of known bacterial species less than 10%. The number of identified viruses reaches approximately 2300 viral species (ICIV 2009), but the likely number could well exceed 150 000, and viruses are evolving constantly. There is therefore also a large deal of unknown.
The taxonomy of bacteria and viruses is more difficult to establish. It must always be kept in mind that a virus species is not only defined by its genetic sequence, but by the whole range of its properties, including pathogenesis. For instance, the same clinical signs can result from infection by many variants of foot-andmouth disease virus; this means that the number of virus strains that may contaminate materials of animal origin is very high. As a matter of fact, the development of new molecular techniques for virus testing has resulted in the discovery of new or known contaminants in vaccines that have been marketed for considerable periods of time.

Vaccine contaminations

The consequences of a vaccine contamination may differ according to the circumstances. It will differ, for instance, according to the nature of the vaccine (attenuated or inactivated), the titre of the contaminant, its degree of inactivation and its pathogenicity. The consequence of a ontamination may be infection (clinical or sub-clinical) of the recipient, and/or a serological response to the contaminant. Smallpox is the first, and so far only, disease that has been eradicated, thanks to vaccination. It is likely that the first vaccines against smallpox were contaminated. Initially, vaccination against smallpox was performed by transmission of a 'naturally' attenuated vaccine, a pox virus of bovine origin (cowpox) from human arm to human arm. This procedure was suspected to transmit syphilis. Later on, a new virus strain, vaccinia, was produced on heifers. Until nearly the end of the 20th century, the vaccine produced in this manner was always contaminated with small amounts of bacteria, and it was accepted by regulatory authorities. The use of cell culture opened a new era for the production of safer human and veterinary vaccines, but was also associated with viral contaminations, especially when using primary cell cultures. At the beginning (between 1954 and 1963), both attenuated and inactivated poliomyelitis vaccines were contaminated with simian virus 40 (SV40), a polyomavirus, from monkeys known to be oncogenic in newborn hamsters. So far, there is no clear evidence of a causal relationship between SV40-containing polio vaccines and cancer in humans. After 1961, manufacturers were required by control authorities to test for the presence of SV40 using infectivity assays and different cell cultures. Vaccine lots found positive for SV40 were no longer released. In 1963, the cell substrate for live oral poliovirus vaccines produced in the USA was changed from primary rhesus monkey kidney cells to primary Cercopithecus monkey kidney cells. This change eliminated SV40 as a potential contaminant of this vaccine's cell substrate, but has intermittently raised concerns about other potential simian adventitious agents, including African green monkey simian cytomegalovirus, which is ubiquitous among Cercopithecus monkeys. In the early 1950s, a new virus was identified as a contaminant in primary monkey kidney cultures used for vaccine production. This virus, called 'foamy virus' (Spumaretrovirinae), induced a characteristic foam-like effect in cell culture, together with the formation of syncitia, leading to cell lysis, and the destruction of the culture batches. Despite these dramatic phenotypic changes in vitro, foamy viruses seem to be harmless in naturally or experimentally infected animals, in which they induce a life-long persistent infection). Other cell lines used for the production of vaccines were also shown to be contaminated, for instance Chinese hamster ovary (CHO) cells were shown to be contaminated with a calicivirus. In the book The River, Edward Hooper tried to demonstrate that trials of vaccines against human poliomyelitis produced in primary cell cultures from chimpanzees (Pan troglodytes), in what is

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now the Democratic Republic of the Congo, introduced human immunodeficiency virus (acquired immune deficiency syndrome) in humans. This has been recently dismissed by phylogenetic studies. Bovine serum, commonly used during vaccine production to provide several biological molecules and growth supporting factors for optimal cell growth, has been the major source of contamination in veterinary vaccines. The most prevalent bovine contaminants have been bovine viral diarrhoea pestivirus ; parainfluenza virus type 3; bovine herpesvirus 1; bovine enterovirus type 4; bovine orbivirus (bluetongue); bovine polyomavirus and bovine parvoviruses. Several incidents linked to veterinary vaccine contamination have been reported. Reticuloendotheliosis virus has been detected as a contaminant of commercial Marek's disease vaccines, and was associated with outbreaks of reticuloendotheliosis in vaccinated chickens. As most of the materials for the production ofMarek's disease vaccines originate from fowl, it was difficult to find the source of contamination. Contaminated classical swine fever vaccines have been responsible for bovine viral diarrhoea virus infections in piglets from vaccinated sows. Vaccines against bovine respiratory syncytial virus infection and vaccines against bovine infectious rhinotracheitis contaminated with bovine viral diarrhoea pestivirus have been at the origin of outbreaks of diarrhoea, and vaccines for pigs contaminated with Circovirus responsible for postweaning multisystemic wasting syndrome [reviewed in [19]). In the early 1990s, bluetongue virus serotype 11 was detected in dogs that had been inoculated with a live, attenuated multi-component canine vaccine contaminated with this serotype ofbluetongue virus. Vaccination of dogs with the contaminated vaccine was responsible for abortion and death in pregnant bitches. It was speculated that the bluetongue virus was introduced into the vaccine via contaminated cells and/or serum used to produce the vaccine. Another spectacular incident was the transmission of scrapie, due to an 'unconventional agent,' to sheep vaccinated with an inactivated vaccine, produced in sheep brain, to protect sheep against louping ill, a brain inflammatory illness spread by ticks. In the 1930s, the use of formalin-inactivated sheep brain as a source for louping ill vaccine led to the transmission of scrapie to over 1000 sheep from one vaccine lot. This list is far from exhaustive. It is nevertheless obvious that the most frequently involved contaminants are pestiviruses, due to the pathogenesis of the infection and the antigenic relationships between the viruses responsible for bovine viral diarrhoea, border disease and classical swine fever. The three main pestivirus species are not only antigenically related, but also can result in crossspecies contamination; there are cytopathic and non-cytopathic strains, and asymptomatic excretors of non-cytopathic strains.

Safety measures

To increase safety, it has been proposed that vaccine virus be cultivated on cells of a species that is different from the species that is the target of the vaccine. However, changing a self-species cell substrate is not always the right solution. For instance, the production of a poultry vaccine in duck cells contaminated with a duck adenovirus produced a new egg drop syndrome in poultry. The production of a pseudorabies (Aujeszky's disease) vaccine in sheep cells contaminated with border disease had detrimental effects on the pig industry resulting from infection and seroconversion against classical swine fever. It thus seems that the species barrier, the idea that it would be difficult or impossible for an infectious agent to pass from one species to another, does not represent protection from crosscontamination. Many infectious agents have been shown to jump the species barrier. In humans, in the final quarter of the twentieth century, more than 30 emerging infections were recognised, the majority of which were of zoonotic origin. Wildlife constitutes an important reservoir of new pathogenic agents for humans and domestic animals.

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Conclusion

Even though there are numerous examples of vaccine contamination, the incidents have been limited, lessons were learned from these incidents and the benefit of vaccination in most cases far exceeds the risk. Vaccine safety has increased with the use of master cell banks of genetically engineered cell lines of mammalian, yeast or bacterial origin; testing and purity control of starting materials and final products; production according to good manufacturing practices and the validation of inactivation processes. However, it should be pointed out that extreme caution is required, and measures must be continuously adapted to an evolving situation.

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