

Zoonotic poxviruses. Summary

Introduction

1. This note provides a brief summary of an analysis prepared by a DISCONTTOOLS group of experts on zoonotic poxviruses. They reviewed the current knowledge on the diseases caused by infection, considered the existing disease control tools, identified current gaps in the availability and quality of the control tools, and finally determined the research necessary to develop new or improved tools. Full details of the analysis can be downloaded from the web site at <http://www.discontools.eu/>.

Disease profile

2. There are multiple zoonotic pathogens within the genus *Orthopoxvirus* (OPV), which includes three virus species of significant consequence to human and animal health. The zoonotic OPVs are:

- vaccinia (VV)/buffalopoxvirus (BPV) affecting bovids, sylvan and peridomestic rodents, and humans;
- cowpox (CoPV) historically associated with dairy cattle, but occurs naturally in sylvan rodents with some spill-over into peri-domestic pests (rats);
- Mpox (MPV) which is a smallpox-like illness in primates, rodents, squirrels and marsupials.

Within certain viral species, most notably cowpox, there is a significant amount of diversity which may contribute to different disease manifestations.

The genus *Parapoxvirus* (PPV) includes three members for which zoonotic transmission has been reported: bovine papular stomatitis virus (BPSV), which infects cattle/camels, pseudocowpox virus (PCPV) affecting cattle/reindeer/dromedaries/humans and orf virus (OV) which can infect sheep/goats/reindeer/muskox/humans. All cause contagious skin infections which are normally self-limiting with low impact on individual animals, although chronic ill health may result from infection. These PPVs are transmissible to humans as diseases considered to be occupational hazards for farmers, shepherds, veterinarians, animal handlers, meat and wool processors and also associated with religious slaughter of animals.

Risk

3. There is likely to be underreporting of the occurrence of zoonotic poxvirus infections worldwide as appropriate diagnostic assays are not readily available, and the stigma attached to producers and hunters due to contact with these agents is considerable. These are classic neglected zoonoses with considerable potential to cause significant, even life-threatening, disease in humans and animals as well as profound negative impacts on agricultural productivity. Prevention and control is normally a combination of vaccination and sanitary / bio-security measures.

Orf virus, a PPV, for example, is in the top twenty most important viral diseases of sheep and goats globally in terms of impact on poor communities. No country has eradicated the disease. For OPVs, the risks for outbreaks of VV/BPV are greatest where traditional, non-mechanised dairy production occurs, but instances of CoPV (which is endemic through much of Eurasia) have also been observed even on mechanised farms. The experience in the United States with zoonotic transmission of MPV, which entered the country via imported exotic animals, underscores the importance of being prepared to manage a potentially catastrophic situation.

Diagnostics

4. ELISAs and PCRs for poxviruses are available but are mostly performed at academic institutions or in public health reference laboratories. Recently however, possibly due to the increase in severe outbreaks of disease, laboratories across Europe, the US, Japan, India and South Africa have shown an increased interest in poxvirus diagnostics, especially Mpox. In most instances this has been to confirm diagnosis of disease outbreaks, thereby reducing the incidence of misdiagnosis with other pathogens causing vesicular disease in ruminants. The specificity and sensitivity of these diagnostic tests needs to be maximised against the global library of virus strains. Equally important would be an assessment of genetic strain variability worldwide to develop accurate diagnostics test that can differentiate between endemic and imported isolates. This may also allow for regional differentiation

and could enhance epidemiological efforts. Species-specific immunological detection reagents are not available for OPVs due to serological cross-reactivity, and rapid and validated pen-side tests are not available. Several laboratories in the EU, including national public health (and defence) laboratories in the UK, Germany, Spain, France and Italy, have the capacity to perform nucleic acid based testing for orthopoxvirus signatures in clinical specimens. Ideally diagnosis with an initial antigen or nucleic acid rapid detection assay would be followed by confirmatory testing at designated reference facilities with the appropriate biocontainment capacity. Ideally, such reference laboratories would include facilities specialising in human and veterinary medical diagnosis. Confirmatory testing should encompass identification of the viral agent to species level.

Vaccines

5. Limited licenced vaccines are available for OPVs, mostly for use against Mpox, and PPVs, orfivirus only, but efficient and safe vaccines providing long lasting immunity are not available. All current vaccines are fully virulent live viruses that can themselves cause outbreaks of disease. No OPV vaccines are under development for specific use in animals. The lack of commercially available products for prevention and control of OPV infections suggests that highly-targeted opportunities exist in this arena, particular for overseas markets in highly affected regions.

It is most likely that protective immunity to OPV requires the stimulation of a cellular immune response. It cannot be predicted if this will be achieved most efficiently by a non-infectious subunit vaccine, an engineered attenuated OPV, or some other means such as a vector containing the appropriate OPV genes. For this reason, it is important to pursue each of these lines of investigation. Viral antigens must be delivered in such a way as to stimulate a cell mediated response. The most promising candidate is nucleic acid-based vaccination.

Pharmaceuticals

6. There are no approved veterinary treatments for poxvirus-related infections but anti-virals have been tested successfully in the laboratory *in vitro* and in lab animals. There has been little consideration thus far of their potential application to the prevention and treatment of neglected poxvirus-associated zoonoses in humans, let alone animals.

Knowledge

7. There are significant areas of uncertainty in the understanding and knowledge of the diseases caused by PPVs, especially in relation to their pathogenesis, immunology, epidemiology and control. . Information is missing about the prevalence and risk factors associated with severe disease, as well as clinical and subclinical prevalence of PPV infections in cattle, red deer and small ruminants in EU member states and the implications of this for public health and livestock production. The possibility of subclinical infections in animals needs to be investigated.

A better understanding of the identity and distribution of reservoirs for zoonotic OPVs is also required. This needs to include identification of i) virus reservoirs (particularly rodent), ii) range of permissive hosts/transmitting hosts, iii) sylvatic transmission cycles and principal opportunities/risks for spill-over. The circumstances surrounding interspecies transmission of OPVs remain largely unknown although they are not thought to be transmissible through contaminated milk products, but definitive evidence is lacking.

Conclusions

No vaccines capable of providing durable sterile immunity for zoonotic poxviruses are available. Obstacles for effective prevention and control of zoonotic poxviruses include an absence of readily available diagnostic assays, a lack of familiarity with the clinical signs of human and animal disease (among physicians and veterinarians), a lack of vaccines and therapeutics to prevent virus acquisition/transmission and the current incomplete understanding of the burden and distribution of zoonotic poxviruses globally. Research in these fields may lead to a reduction in the incidence, and therefore in the impact, of poxvirus-associated disease. This will not only have benefits for the health and welfare of affected animals, but should also reduce the zoonotic impact on human health.