DISCONTOOLS

Orthopox viruses.
Summary

Introduction

1. This note provides a brief summary of an analysis prepared by a DISCONTOOLS group of experts on orthopox viruses (OPV). They reviewed the current knowledge on the disease, 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/ by selecting Disease Database, then the specific disease and highlighting the variables of interest. This is completed by selecting "create a report" which can then be downloaded as either a PDF or Excel spread sheet

Disease profile

2. There are multiple zoonotic pathogens within the genus Orthopoxvirus (OPXV) which includes three virus species of significant consequence to human and animal health. These are vaccinia virus/buffalopox virus (VV/BPXV), cowpox virus (CPXV), and monkeypox virus (MPXV). Within certain "species" most notably cowpox, there is a significant amount of diversity which may contribute to different disease severity or disease manifestations. The zoonotic OPXV are: VV/BPXVs scabby lesions and ulcers affecting bovids/ sylvan and peridomestic rodents, and rodents/humans. An outbreak of VV was recently described in horses in Brazil. Cowpox (CPXV) - Pustular rash and fever - historically associated with dairy cattle, but occur naturally in sylvan rodents (voles, wood mice, gerbils) with some spill-over into in peri-domestic pests (rats). Observed in cattle (now rare) humans, domestic felines /zoo animals/rodents. .Occasionally observed in housecats, exotic felids, elephants, rhinoceros, horses and okapis. Foxes are also suspected to be susceptible. Monkeypox (MPXV) is a smallpox-like illness with disseminated pustular rash and fever in primates/ rodents squirrels and marsupials

Risk

3. There is likely to be underreporting of the occurrence of zoonotic poxvirus infections worldwide as appropriate diagnostic assays are not readily available. Risks for outbreaks of VV/BPXV are greatest where traditional, non mechanized dairy production occurs, but instances of CPXV (which is endemic through much of Eurasia) have also been observed even on mechanized farms. BPXV/VV is known to cause substantial economic losses in regions such as Brazil, India, and Saudi Arabia. The spread of VV/BPXV may have a devastating impact on rural, artisanal dairies where production depends on a small number of cows or buffaloes. The experience in the United States with zoonotic transmission of MPXV, which entered the country via imported exotic animals, underscores the importance of being prepared to manage a potentially catastrophic situation.

4. Recent human Orthopoxvirus infections in the EU have been in pet owners, zoo workers and veterinarians. Infections have either direct contact with infected rats, or contact with other animals (elephant, cat) that had presumably become infected following contact with a rat or another small rodent harbouring CPXV. Infections with VV/BPXVs or CPXV can be life-threatening in immune-compromised subjects. MPXV infections in people result in the development of a smallpox-like illness with fever, prostration and disseminated pustular rash. Human infection with Congo Basin variants of MPXV are fatal up to 15% some of the time.

Diagnostics

5. Antibody responses to old world Orthopoxviruses are broadly cross reactive. Species specific immunological detection reagents are not available. At present there are no robust or commercial antibody tests in use for poxviruses and this can lead to misdiagnosis with other pathogens causing vesicular disease in ruminants. 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 the presence of orthopoxvirus signatures in clinical specimens.

6. Antigen or nucleic acid-based rapid detection assays would likely be preferable and of greater utility than screening tests designed to detect orthopoxvirus antibodies in serum. The former could be

run using lesion material as clinical diagnostic specimens. Confirmatory testing could be performed at designated reference facilities having appropriate biocontainment capacity. Ideally, reference laboratories would include facilities specialising in human and in veterinary medical diagnosis. Confirmatory testing should encompass identification of the viral agent to species level (e.g. vaccinia virus vs. monkeypox virus) which is typically accomplished through nucleic acid-based analysis (i.e., PCR, DNA sequencing).

7. A better understanding of protein and nucleic acid level differences between OPX viruses and within OPX species would allow for the development of rapid diagnostic tests that could distinguish between agents and identify viruses to strain type. An understanding of the precise clinical profiles of the different infections along with risk factors for human and animal infection would support the development of clinical algorithms to identify suspected cases and to guide appropriate application of any diagnostic testing.

Vaccines

8. Vaccines against OPXV-associated zoonoses should provide durable cross-protection against infection with multiple species and should pose little to no risk of transmission between humans. Vaccines for prevention of OPXV infection in animals are currently unavailable and none are currently thought to be under development for specific use in animals. There is a need to improve vaccines against these viruses since current vaccines are fully virulent live viruses that can themselves cause outbreaks of disease. The lack of commercially available products for prevention and control of OPXV infections suggests that highly-targeted opportunities exist in this arena, particular for overseas markets in highly affected regions.

9. It is most likely that protective immunity to OPXV requires the stimulation of a cellular response. It cannot be predicted if this will be achieved most efficiently by i) a non-infectious subunit vaccine, ii) an engineered attenuated OPXV, or iii) some other means such as a vector containing the appropriate OPXV genes. For this reason it is important to pursue each of these lines of investigation. Delivery of viral antigens in such a way as to stimulate a cell mediated may be of considerable importance. The most promising candidate may be the use of DNA vaccination

Pharmaceuticals

10. There are no approved veterinary treatments for poxvirus-related infections but anti-virals have been tested successfully in the laboratory. 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

11. A better understanding of the identity and distribution of reservoirs for OPXV associated zoonotic agents is 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 rodent reservoirs for CPXV (and VV) are undefined on the European continent impeding fundamental control measures. The circumstances surrounding interspecies transmission of OPXV remain largely unknown although they are not thought to be transmissible through contaminated milk products, but definitive evidence is lacking. There are no published studies on the costs of PPV and OPXV diseases in the EU and worldwide. Full details of the gaps are shown in the Disease and Product analysis for OPV on the DISCONTOOLS website.

Conclusions

12. Recent gains in diagnostic and treatment capacity for OPXV infections engendered through bio-terror preparedness activities could be leveraged to combat the negative health, welfare and economic impacts of zoonotic OPXV including VV/BPXV, CPXV and MPXV. Preparation includes having (1) trained clinicians who can identify suspected cases of OPXVs-associated illnesses in humans and animals, (2) diagnostic testing capacity to rapidly identify an poxvirus-associated aetiology and further to identify the species of virus involved, (3) implementation capacity for appropriate sanitary measures, which may include quarantine and vaccination, and (4) therapeutic

treatments available for persons experiencing severe illness due to infection with any one of these agents.