What significance do helminths species-complexes have for the prevention, diagnosis and treatment of human infections?

Paiboon Sithithaworn, Trevor N. Petney and Ross H. Andrews

Department of Parasitology and the Liver Fluke and Cholangiocarcinoma Research Centre, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; Cholangiocarcinoma Screening and Care Program (CASCAP), Khon Kaen University, Khon Kaen, 40002, Thailand; Institute of Zoology, Department of Ecology and Parasitology, Karlsruhe Institute of Technology, Komblenzstrasse 13, Karlsruhe, Germany; Faculty of Medicine, St Mary’s Campus, Imperial College London, UK

*Corresponding author: Tel: +66 43 348387; E-mail: paibsit@gmail.com, paib_sit@kku.ac.th

Received 28 February 2015; revised 19 March 2015; accepted 20 March 2015

Keywords: Cryptic species, Parasite infections, Species complex

With the application of increasingly sophisticated molecular tools to the study of systematics (taxonomy, phylogeny), a multitude of new, initially genetically defined species have been uncovered, while molecular sequence data, including ‘bar-coding’ of the ITS-2 and cox-1 genes, allow species identification and the discovery of cross-host species interactions. Cryptic species are typically genetically definable entities that occur within a taxon previously recognized as a single morphologically defined entity. This is the case with many medically important macroparasite species, which we now know to be separate taxa but which are very difficult or cannot be determined morphologically. Historically, unraveling the species complexes within the mosquito genus Anopheles provides a good example of the importance of recognizing cryptic species as different; morphologically near identical species have different capacities for transmitting malaria leading to the confusing situation of the presence of supposed Anopheles vectors without malaria.

With the recognition that the areas without malaria were occupied by non-vector cryptic species this problem was solved and control and screening programs could be concentrated in those areas with known vectors.

The situation with helminths is in most cases less clear, although numerous species complexes are known. These include trematodes such as Opisthorchis viverrini sensu lato (s.l.) and Paragonimus westermani s.l., members of the Echinostomatidae, and possibly Schistosoma japonica, cestodes such as Echinococcus granulosus s.l., as well as nematodes from the genera Anisakis and Pseudoterranova. Once the genetic differences between the species have been determined, studies have shown that biological differences, for example in host usage, life cycle parameters, such as fecundity, and morphology, also occur, confirming the molecular data. Thus, we have a situation in which treatment options based on the original single species paradigm are, in fact, used for multiple, albeit related, species. How important is this in determining options for the prevention, diagnosis and treatment of the human diseases caused by these parasites?

In the case of some genetic groups within the P. westermani complex from Thailand, India and Sri Lanka the answer to this question is simple; they do not infect humans so that no initial diagnosis in humans can be made. For other groups the answer is more complex.

One of the best studied examples is the E. granulosus species complex. What was originally defined as E. granulosus is now considered to consist of at least five species containing 10 genotypes, E. granulosus sensu stricto (s.s.), E. canadensis, E. equinus, E. felidis and E. ortleppi. The majority of human cases are caused by E. granulosus s.s. with 11% being caused by E. canadensis, rare cases by E. ortleppi and none by E. equinus or E. felidis. Although most of these species occur sympatrically over much of their range, they differ from one another in their life history strategies, particularly for intermediate hosts, and therefore the transmission dynamics varies considerably between species. This, together with differences in antigenicity, sensitivity to chemotherapy agents and pathology, clearly indicate that the options for prevention, diagnosis and treatment need to be clearly defined and differentiated for each species.

For O. viverrini s.l., the most severe form of disease associated with opisthorchiasis is cholangiocarcinoma (CCA), which can take several decades to develop since the mean age of CCA patients is about 50 years. The cancer initiation process, i.e., DNA damage, may be initiated directly after infection, but the carcinogenesis process may continue for several years with or without the
The continued presence of parasites is an important consideration for the continued presence of parasites in the context of the systematics and the incidence of cholangiocarcinoma. The systematics and the incidence of cholangiocarcinoma are well known to vary geographically in northeast Thailand. Members of the O. viverrini complex are also geographically separated into different watersheds. The possibility of cross infection of human by parasites from different wetlands should be high although very little is known about the pathway of fish from the point of harvest in reservoirs to the point of consumption. Re-infection may occur presumably by mixtures of different parasite genotype from different wetlands, consequently the current genotype that is infective may not be the initial cause of the pathogenesis. Knowledge that some species within the O. viverrini complex are more pathogenic than others would allow screening to be concentrated in the areas where these species are present. Here, however, the relationship between the pathology of the disease and the infective agent remains unclear, although such knowledge is essential for current programs aimed at the early detection of cholangiocarcinoma so that curative surgical resection is possible, for example the Cholangiocarcinoma Care and Prevention Program based at Khon Kaen University in Thailand.

The correct identification of a species is critical to both basic and applied research. The recognition of cryptic species has implications far beyond the taxonomic level. Biological work of any kind done prior to the definition of these species will be unreliable unless material is still available allowing for definitive identification; this is particularly important for sympatric or parapatric members of the species complex for which geographical location alone does not suffice to define the species present. From the medical point of view, there are numerous potential problems. Are there differences in virulence within the species complex? Does molecular diagnosis work for all species? Is the susceptibility to drugs the same? Has resistance to drugs developed in some species but not others? Which hosts must be considered in control programs? What should be explained in education programs? What levels of morbidity and mortality are associated with each cryptic species?

If two or more species are confused under a single name, then the data collected may well refer to a mixture of different species or to the wrong species, leading to the choice of false diagnostic and treatment options. Thus the recognition of parasite species complexes, outside of the specialist groups working on them, should be a general medical priority.

**Authors’ contributions:** PS, TNP and RHA contributed to writing this paper. All authors read and approved the final manuscript. PS is the guarantor of the paper.

**Funding:** We acknowledge the support of the Basic Research Grant, Thailand Research Fund and Office of the Higher Education Commission, through the Center of Excellence in Specific Health Problems in Greater Mekong Subregion Cluster (SHeP-GMS).

**Competing interests:** None declared.

**Ethical approval:** Not required.

**References**


