

January 21, 2007

Applicant: **Sourya Shrestha**

Mentor/Faculty Recommender: **Aaron A. King**

To whom it may concern:

I write to heartily recommend Sourya Shrestha for inclusion in the **US-Africa Advanced Studies Institute on Mathematical Modeling of Infectious Diseases in Africa**. Sourya is a student in the graduate Applied Interdisciplinary Mathematics program here at the University of Michigan. He has recently achieved candidate standing.

Sourya has been working with me for a year now on what I believe to be a very promising project on the *Bordetella* diseases (whooping cough in humans, kennel cough in dogs, atrophic rhinitis in pigs; these bacterial pathogens infect the respiratory tracts of a wide range of mammals). The goal of this research, which we are conducting in cooperation with Eric Harvill and Ottar Bjørnstad of Penn State, has been to understand the mechanisms behind the emergence of *B. pertussis* and *B. parapertussis*, which produce extremely acute infections in humans, from a *B. bronchiseptica*-like ancestor, which likely produced persistent infections in ancient humans in the way that *B. bronchiseptica* does today in humans and many other mammals. We take as our starting point the detailed understanding of the interactions of the pathogens with their hosts' immune systems that has emerged in recent years. We begin by writing low-dimensional mechanistic models for the within-host pathogen dynamics and for the dependence of between-host transmission on pathogen load. From this foundation, we examine the consequences of various pathogen strategies on fitness at the population level.

In a proof-of-principle study, we showed that increasing host population densities favor the evolution of more acute infections. Moreover, for host populations below a critical threshold, pathogen evolution can take the pathogen to the edge of its own extinction; above the threshold, the optimal pathogen strategy is buffered from extinction. These results (to be submitted for publication in the near future), give us reason to believe that a more careful study of the *Bordetella* diseases from this perspective is warranted. We intend to explore the within-host dynamics, transmission mechanisms, and metapopulation aspects of this problem in much greater detail. The potential outcomes of this study are large. First, the study has the potential to yield general insights into one of the tradeoffs that is potentially operative in many emerging infectious diseases. Second, the approach of deriving the epidemiological consequences of in-host pathogen dynamics is in principle applicable wherever sufficient immunological information can be obtained.

Sourya is a competent mathematician with facility in deterministic and stochastic dynamics. He can readily assimilate biological information and seems to have a decent and improving intuition for biological dynamics. He is enthusiastic about solving puzzles of disease dynamics. He is interested in understanding host-pathogen coevolution through detailed analysis of specific systems.

I believe that participation in the Advanced Studies Institute will be highly beneficial for Sourya and for the other participants. Sourya will benefit from exposure to the phenomenology of other diseases and to the approaches others are taking to the modeling of these systems. I imagine it is likely that others will appreciate the approach Sourya has been taking in the project described above.

Sourya hails from Nepal. Although we have not discussed his post-graduation plans, my sense is that there is much to be gained by training developing-world scientists in the most sophisticated approaches to infectious disease modeling. [As an aside, I assure you that Sourya's English skills are not substantially below those of a native.]

It goes without saying that I am willing to continue mentoring Sourya in the research he has begun and in any additional projects that arise from his participation in the Institute. I do hope you will give full consideration to his application. If you have any questions, please don't hesitate to contact me by email at *kingaa@umich.edu*.

Sincerely,

Aaron A. King
Assistant Professor of Ecology & Evolutionary Biology and Mathematics
University of Michigan