# Expanding the Definition of Infectious Disease

## A Review of HIV & Schistosomiasis

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*Abstract*

Over the past century, as the field of public health adopted new actors and new priorities, the definition of infectious disease expanded, yielding new ideas on controlling and treating disease. In its primary form, infectious disease referred to a collection of symptoms resulting from infection by a single pathogen. As this definition expanded, it incorporated upstream causes such as poverty, access to health infrastructure and stigma. However, we must now adopt an even more expansive definition of infectious disease that integrates symptoms stemming from a collection of pathogens and a collection of upstream factors. Human immunodeficiency virus (HIV) and schistosomiasis illustrate the importance of recognizing the interactions that exist between different infections. In this specific case, as upstream factors lead to infection by one pathogen, the risk of transmission of the other diseases increases almost three-fold. As we move into the future and develop new interventions, control mechanisms are needed to combat specific pathogens, their upstream factors, *and* their interactions with each other. Once we accept that illness is affected by a combination of different infections, we can develop more effective treatments and public interventions to: 1) further prevent disease, 2) prolong life, and 3) promote health.

*Introduction*

In the Acheson Report of 1988, the United Kingdom Health Department defined public health as "the science and art of preventing disease, prolonging life and promoting health through the organized efforts of society." This definition, also adopted by the World Health Organization (WHO) in their Health Promotion Glossary, illustrates how the field seeks to improve the lives of not only individuals but also populations across the world through the prevention of disease (1998). One key aspect of this idea of public health is defining "disease" and using that definition to determine how to best treat and decrease the burden of infectious disease on populations. The definition of infectious disease has progressed through two stages as public health has developed. By analyzing these two stages of public health and examining their shortcomings, using schistosomiasis and HIV as case studies, it is clear that a third, all-encompassing definition must be adopted to increase the impact of public health interventions.

*Background of Schistosomiasis*

Schistosomiasis, once called bilharzia, is a chronic disease caused by one of three different blood fluke trematodes, or parasitic *Schistosoma* worms (National Center for Health Marketing [NHCM], 2010). *S. mansoni* and *S. japonicum* cause the intestinal disease, and *S. haematobium* causes the urogenital one (Wu & Halim, 2000). Schistosomiasis is found across the globe in over 70 countries, but it is most commonly seen in impoverished tropical and sub-tropical locations (NHCM, 2010). While the disease was initially concentrated in rural areas, as the result of migration and insufficient sanitation schistosomiasis now affects urban environments as well, particularly those with populations of low socio-economic status (WHO, 2011). An estimated 700 million people worldwide are at risk of contracting schistosomiasis, and more than 207 million are already infected (WHO, 2011).

Transmission of schistosomiasis occurs when a human's skin comes in contact with freshwater contaminated with schistosome-carrying snails (Ross et al., 2007). In the early stages of infection, a rash or slight itch develops followed by coughing and muscle aches (Wu & Halim, 2000). The intestinal version typically results in abdominal pain, diarrhea, blood in the stool and an enlarged liver. It is diagnosed by testing for the presence of *Schistoma* eggs in feces (Ross et al., 2007). The urogenital version often presents itself with fibrosis of the bladder, kidney damage and even bladder cancer; it is diagnosed by analyzing blood in urine, or hematuria (Poggensee & Feldmeier, 2001). In women, the urogenital type may result in genital lesions, vaginal bleeding, pain during intercourse and nodules in the vulva (Poggensee et al., 2000). In men, this type may also cause damage in seminal vesicles and the prostate, though this remains unproven (Poggensee, Kiwelu, Saria, Richter, Krantz, & Feldmeier, 1998). The symptoms listed above often incapacitate individuals, preventing them from fulfilling their social and financial responsibilities. While schistosomiasis can easily be treated by praziquantel, an effective low cost method with few side effects, less than 10% of those in need of the drug presently have access to it (End the Neglect, 2011).

Although transmission is restricted to areas with contaminated water, it is difficult to stop at-risk populations from carrying out basic domestic tasks such as bathing and wash-

ing clothes in contaminated areas. These tasks put women and children especially at risk (NCHM, 2010). Schistosomiasis, like many neglected tropical diseases (NTDs), historically has received little international attention, limiting both scientific research and funding for treatment. While schistosomiasis has a burden of 4.6 million disability adjusted life-years (DALYs), the disease is often forgotten because of its relatively low mortality rate (280,000 people per year). Fortunately, metrics such as the DALY have helped place schistosomiasis and other NTDs on the list of global priorities in recent years (King & Dangerfield-Cha, 2008).

## *Background of Human Imunnodeficiency Virus (HIV)*

Acquired Immunodeficiency Syndrome (AIDS) is a group of symptoms caused by the human immunodeficiency virus (HIV) that limits the body's ability to combat disease (Mayo Clinic Staff [MCS], 2008). Normally, white blood cells and antibodies—coordinated by CD4 lymphocytes, or helper T-cells—attack foreign particles in order to protect the body (Roederer, 1998). Upon infection with HIV, the virus attaches to CD4 lymphocytes, enters the cells and begins reproducing (Autran et al., 1997). After a period of replication, the large amount of HIV virus cause the CD4 lymphocytes to burst, killing the cells and releasing the multiplied virus into the bloodstream (MCS, 2008). As these newly created virus particles attack other CD4 lymphocytes, the immune system begins to shut down. If left untreated, billions of HIV-particles can be produced every day, giving the patient a life expectancy of less than ten years (MCS, 2008).

In 2008, 33.4 million people were living with HIV; 2.1 million were children under the age of 15 years (UNAIDS, 2010). 2008 saw 2.7 million new infections with 2.0 million deaths caused by AIDS, almost 300,000 of which were children under the age of 15 (UNAIDS, 2010). HIV is not distributed evenly across the globe. An estimated 22.5 million people are living with HIV in sub-Saharan Africa, accounting for roughly 67% of the global HIV presence (UNAIDS, 2010). In 2009, 1.3 million people died from AIDS, and 1.8 million new infections were transmitted in sub-Saharan Africa alone (UNAIDS, 2010). Because of its widespread effects, HIV is a priority for research and treatment across the globe.

HIV is transmitted via the mixing of bodily fluids such as blood, semen, or vaginal excretions (Bouvet, Grésenguet & Bélec, 1997; Fiore et al., 1995). It is most commonly passed on through unsafe sexual contact, transfusions with infected blood, needle sharing or mother-child interaction during pregnancy (Santmyire, 2001; Davis & Weller, 1999; Romanelli, Smith, & Pomeroy, 2000). While available diagnostic tests have high specificity once the virus has initiated an immune response, a diagnosis within the first twelve weeks is rare (MCS, 2008). Indeed, some infected patients do not test positive for HIV until six months after infection, complicating control mechanisms (MCS, 2008).

While new treatments for HIV are being researched constantly, highly active anti-retroviral therapy (HAART) is the main treatment in use today. HAART reduces the amount of virus in one's blood to very low or even undetectable levels (Roederer, 1998). This therapy, or cocktail of therapies, is typically comprised of three drugs from at least two different classes of treatment (MCS, 2008).

Many populations across the globe still lack access to both HIV diagnosis and treatment due to high costs (Cheng, Landay, & Miller, 2008). Furthermore, when diagnosis and treatment are available, access is often unreliable and favors some sub-communities over others (Cheng et al., 2008). The stigma associated with HIV as a sexually-transmitted infection (STI) often prevents individuals from getting tested for HIV and, if they are tested, from disclosing the results (Alonzo & Reynolds, 1995; Chan, Yang, Zhang, & Reidpath, 2007; Sambisa, Curtis, & Mishra, 2010). This lack of personal knowledge and disclosure heightens the harmful effects of the disease across the globe by increasing infection rates, particularly in high-risk areas such as sub-Saharan Africa (Sambisa et al., 2010).

## *Model #1: One Disease, One Pathogen*

Stedman's Medical Dictionary, one of the most trusted sources for medical definitions, defines infectious disease as "an interruption, cessation, or disorder of a body, system or organ structure or function resulting from the presence and activity of a microbial agent" (2000). Using this definition, the combination of symptoms associated with the body's response to infection by one of *schistoma* worms and its eggs is known as schistosomiasis. By the same token, the body's symptomatic response to infection by HIV is known as AIDS. Such a definition assumes that for every infectious disease there exists only one cause: the pathogen. With one cause, there can be only one type of intervention: removal of the pathogen. Such treatment entails administration of a medication that somehow inhibits this pathogen's biological function.

Such a mentality, as Joseph Lederberg and Adel Mahmoud argue, creates a war-like mindset in which humans must build up arsenals and ammunition against infections in order to inhibit pathogens' function and thus cure disease (Lederberg 2008; Mahmoud, 2010). Indeed, as illustrated in Marcos Cueto's description of malaria treatment in Mexico, such an approach is less than adequate; *magic bullet solutions* or interventions based on administration of medication have rarely seen success (Cueto, 2008). Scientifically, *magic bullet solutions* create a war, as Ledererburg introduces, between "our [humans'] wit and their [pathogens'] genes" (Lederberg 2000). While humans may be able to successfully combat pathogenic genes in their stagnant form, the introduction of the added variable of mutation complicates the story. Furthermore, dependence on treatment to cure disease is incredibly expensive. Mahmoud argues that even after a drug has been discovered, pharmaceutical companies such as Merck and GlaxoSmithKline can still spend a further $1 billion on specific analysis and product testing (Mahmoud, 2010).

Much of the challenge in *magic bullet solutions* is social. Simply administering medications to populations does not take into account the patients' perceptions of the disease or of the medication itself. There may be underlying prejudices toward the medication or its administration; side-effects could also elicit major social responses, inhibiting the effectiveness of a medication-based solution. Finally, using drugs to combat disease is truly nothing more than a "band-aid solution." Not only can a second exposure renew the infection and thus the disease, but pharmaceutical treatment does little to remove the cause of the infection.

Interventions against schistosomiasis, while effective to

some degree, have been entirely dependent on public-private partnerships (PPP) that distribute the drug praziquantel, with little to no focus on prevention. In 2007, Merck Pharmaceuticals Inc. partnered with the WHO to help combat schistosomiasis in African school children, providing 200 million tablets of Cesol® worth roughly $80 billion for the treatment of 27 million children (The Merck Group, 2011). The Schistosomiasis Control Initiative, a joint program of the Bill and Melinda Gates Foundation, MedPharm, Imperial College London, the Harvard Center for Population & Development Studies and the WHO also provided 13.7 million tablets of praziquantel to three countries in East Africa and three countries in West Africa (MedPharm, 2011).

While it would be unfair to argue that the aforementioned treatment-based intervention had no effect in reducing the burden of schistosomiasis, the long-term potential of programs like this is certainly limited. Even with treatment available, over 700 million people across the globe are still at risk of contracting the disease. So long as clean water is inaccessible, schistosome larvae will still infect individuals (WHO, 2011). Furthermore, Smits et al. argue that the risk of creating resistance is particularly high when treating diseases such as schistosomiasis with only one known treatment (2009). Reports of resistance to praziquantel have already been published, indicating that the long term-potential for dependence on this treatment is limited (Botros & Bennett, 2007).

Stedman's definition of infectious disease, based solely on a microbial agent infection, is problematic. Such a definition implies that the sole method of reducing mortality and morbidity is through treatment. However, dependence on *magic bullet solutions* is not only expensive, but also has little potential for long-term success. These limitations, found not only in the case of schistosomiasis but also in other diseases, have led to the establishment of a new, more expansive, generally accepted definition of infectious disease.

### *Model #2: One Disease, One Pathogen, Multiple Upstream Factors*

Between 1900 and 1999, the average lifespan of Americans increased by more than 30 years; of that increase, 25 years have been directly attributed to advances in public health preventative measures (NCHM, 2010). Improvements in water purification and sanitation led to decreases in typhoid and cholera infections, which were major causes of illness and death in the early 20th century (NCHM, 2010). The importance of successful public health programs implies a more expansive definition of infectious disease than that discussed in Model #1. The success that preventative measures such as water sanitation and increased hygiene have had in decreasing transmission of disease pathogens shows that infectious disease is not solely "an interruption, cessation, or disorder of a body, system or organ structure or function resulting from the presence and activity of a microbial agent" as described by Stedman, but also a result of a series of upstream factors and social determinants.

Unlike the first model, in which infection by a pathogen was the only cause of disease, this definition recognizes other, indirect causes. This definition accepts both downstream causes (which directly catalyze the infection) and upstream ones (indirect causes of infection, such as water sanitation, hygiene and stigma). By accepting that a series of different factors may result in disease, we can construct a better strategy of combating disease.

While this definition is better than the first, it still limits the maximum effect that public health interventions can have on reducing mortality and morbidity. This definition does not address the effects of interaction between multiple diseases. Preventative interventions are rooted in inhibiting the actual infection and the causes that may lead to that infection. However, they do not deal with the interaction between different pathogens. Analysis of HIV control mechanisms in South Africa reveals that even with this more expansive definition of disease, mortality and morbidity are still unacceptably high.

Following almost five years of direct AIDS denialism (the view that HIV does not lead to AIDS) led by South African President Thabo Mbeki in 2004, full HAART treatment was finally offered to all South Africans in need, free of charge (AVERT, 2010). Furthermore, South Africa has introduced primary prevention by distributing information on *Abstinence, Being Faithful and Condom Usage* (ABCs) (South African Department of Health [SADH], 2007), and has created nation-wide Volunteer Counseling and Testing (VCT) centers that, in theory, reach every citizen of the country. A bureaucracy composed of a National AIDS Council, Provincial AIDS Council, and even Local AIDS Councils, has been established in order to integrate the efforts of government, non-profit non-governmental organizations (NGOs), faith-based organizations and the private sector (SADH, 2007).

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When discussing the case of HIV in South Africa, recognizing the harmful impact of President Mbeki's denialism is important. When forming his Presidential AIDS Advisory Panel in 2000, Mbeki appointed a number of AIDS denialists, which greatly impacted his government's approach to the infection (Schoofs, 2000). In response, the global scientific community formed the Durban Declaration in 2000, which confirmed that HIV in fact leads to AIDS, and was signed by over 5,000 research scientists (Durban Declaration, 2000). Two independent research studies from University of Cape Town and Harvard University concluded that Mbeki's denialist policies led to the premature death of more than 330,000 South Africans (Chigwedere, Seage, Gruskin, Lee, & Essex, 2008; Nattrass, 2008). Without question, the single largest hindrance to HIV treatment and prevention in South Africa was Mbeki's denialist policies. Fortunately, the Treatment Action Campaign, led by Zachie Achmat, became the unified pro-HAART voice for South Africans, and through significant domestic and global lobbying, finally persuaded the South African government to recognize the connection between HIV and AIDS (AVERT, 2010).

Despite the ongoing efforts to treat both downstream and upstream causes with full governmental support, an estimated 5.7 million people still live with HIV in South Africa, where an estimated 250,000 citizens died of AIDS in 2008 (AVERT, 2010). Almost one in every three women between the ages of 24 and 29 and over a quarter of men between the ages of 30 and 34 are HIV positive (AVERT, 2010). Even after inhibitory governmental policies were reversed, HIV incidence and AIDS-related mortality has still not been significantly reduced in South Africa.

Even in areas where infection rates have decreased, such as Brazil, we must be critical of these apparent successes, as Joao Biehl argues in *Will to Live* (2007). Rather than judging success solely on epidemiological prevalence and incidence data, Biehl uses anthropological narratives to show a different view of HIV in Brazil (Biehl, 2007). In his anthropological study, Biehl illustrates how individuals are still suffering greatly in Brazil from HIV, despite what has been named as one of the most successful HIV-control efforts in history (Biehl, 2007).

Because the present definition of infectious disease and resulting interventions are not doing enough to fight disease, a broader definition should be employed. The new definition should result in interventions that target how a number of infections deleteriously interact with one another, in addition to downstream and upstream factors.

### *Model #3: One Disease, Multiple Pathogens, Multiple Upstream Factors*

This third model defines disease as an interruption, cessation or disorder of a body, system or organ structure, or a function resulting from the presence and activity of a number of microbial agents that could be the result of a series of upstream factors. This definition implies that infectious disease may not be caused solely by one infection, or even just the upstream factors that lead to that infection; rather, this new definition also takes into account how infection by one pathogen increases the susceptibility to another.

In a cross-sectional study of rural women in Zimbabwe, a multivariate analysis concluded that infection with *S. haematobium*, the urogenital version of schistosomiasis, increased a woman's risk of contracting HIV by 190% (Kjetland et al., 2008). This initial study and conclusion started a whole new sub-field of HIV research: analyzing the interaction between schistosomiasis and HIV.

There is significant overlap between upstream causes of both infections. Indeed, impoverished populations that lack access to clean water, sanitation and basic health infrastructure are at the highest risk of contracting both diseases (WHO, 2011). In terms of distribution, Sub-Saharan Africa and the tropical parts of South America have the highest rates of both infections (NCHM, 2010). While HIV and schistosomiasis carry different specific stigmas, they both have many social repercussions. If untreated, both pathogens can be fatal and can incapacitate a person to the point of inhibiting them from fulfilling their social, familial and financial responsibilities.

Beyond these upstream comparisons, a biological connection directly links the two. As introduced earlier, *S. haematobium*, the urogenital version of schistosomiasis, accounts for approximately two-thirds of all cases of schistosomiasis (WHO, 2011). Of the estimated 112 million cases of *S. haematobium* infection in sub-Saharan Africa, 70 million result in hematuria, or blood in the urine (King & Dangerfield-Cha, 2008). Between 33% and 75% of females infected with this urogenital form of schistosomiasis will also suffer from a sub-form of the disease, female genital schistosomiasis (FGS) (Fenwick et al., 2009). FGS is caused by the deposition of *schistoma* eggs in the uterus, cervix, vagina or vulva; deposition typically results in inflammation comprised of granulomas, fibrosis and angiogenesis (Van Der Werf et al., 2003; Poggensee & Feldmeier, 2001). This inflammation often leads to a buildup of genital pathognomonic genital lesions, or wounds of the genital region (Poggensee & Feldmeier, 2001). These lesions in turn manifest themselves as mucosal grainy sandy patches typically accompanied by bleeding and abnormal vascularization (Kjetland et al., 2008).

These sandy-patches, likely due to increased friction on already degraded cervical and vaginal tissues, increase the likelihood of HIV transmission during sexual intercourse (Ndhlovu et al., 2007). Genital schistosomiasis can also induce chronic inflammation of the pelvic region in men. Drawing parallels with bacterial urethritis, it can be hypothesized that there will be increased viral shedding in the semen of co-infected males, further increasing the probability of transmission (Harms & Feldmeier, 2002). Therefore, infection with schistosomiasis biologically increases the risk of transmission of HIV in both men and women. While dissemination of condoms and other HIV-specific interventions may have a larger impact on reducing the transmission of HIV, treating schistosomiasis decreases the risk of transmission of HIV, thereby having a dual impact.

A prospective cohort study was conducted in Zambia that tested the effect of HIV infection on the effectiveness of praziquantel, the drug used to treat schistosomiasis. The study demonstrated that the presence of HIV had no effect on the effectiveness of praziquantel at targeting schistosomiasis (Mwanakasale et al., 2003). That being said, schistosomiasis treatment does have an effect on HIV treatment. In an immunological study in Europe, results showed that schistosomiasis treatment attenuates HIV replication by decreasing systemic inflammation (Erikstrup et al., 2008). This finding implies that treating schistosomiasis in HIV patients has a more expansive impact – the treatment not only helps cure schistosomiasis, but it also helps treat HIV by inhibiting its replication (Erikstrup et al., 2008).

At the community level, educational interventions that describe how different pathogens interact with each other should be offered to children. In communities where health education is already offered, curricula should be adapted to emphasize how infectious disease is caused by a multitude of pathogens and social determinants. In communities where health education is not yet offered, awareness campaigns that currently disseminate information specific to one pathogen should be replaced by campaigns that illustrate how pathogens endemic in that area interact with each other. Specific to the interaction between schistosomiasis and HIV and in addition to other public health measures such as water sanitation, mass-prophylactic praziquantel treatment should be provided to young girls in school (Lillerud, Stuestoel, Hoel, Rukeba, & Kjetland, 2010). By inhibiting infection of all girls with schistosomiasis and thus FGS, the risk of increased HIV transmission due to genital legions is inhibited. In this case, the treat-

ment acts as a preventative therapy for both schistosomiasis and HIV. In their editorial entitled "Africa's 32 Cents Solution for HIV/AIDS" in *PLoS*, Hotez et al. argue that the funding ear-marked for use in combating diseases such as HIV, malaria and TB, should be used to pay for mass-treatment of all young girls in co-endemic areas (Hotez, Fenwick, & Kjetland, 2009).

Schistosomiasis and HIV, like many other infections, should be treated and discussed together. More expansive treatment and education can be developed only if we adopt a definition in which disease is a group of symptoms caused by multiple pathogens and upstream factors.

## *Conclusion*

In the ever-changing world of public health, the focus on improving population health has remained constant. Part of the growing complexity has involved the expansion of the definitions of disease control and treatment. In its earliest form, infectious disease referred to an illness that stemmed from infection by a single pathogen. This definition limited the scope of public health interventions and thus was later expanded to include upstream causes. As we move into the future, we must accept an even more expansive definition of infectious disease: one in which illness is characterized by symptoms that stem from a collection of pathogens and a collection of upstream factors. HIV and schistosomiasis illustrate the importance of recognizing the interactions between different pathogens.

This study, however, showcases just one of the many interactions that exist between different disease pathogens. As a disease that directly inhibits the immune system, HIV and the resulting CD4 inhibition directly increase one's susceptibility not only to other high burden infections such as tuberculosis and malaria, but also to more opportunistic infections (Gladwin & Trattler, 2011). Those with HIV are between 20 and 37 times more likely to be co-infected with TB than the baseline population (WHO, 2010). Furthermore, HIV predisposes one to complications associated with other viral infections such as cytomegalovirus, bacterial infections including cryptococcosis, as well as fungal infections caused by *Microsporum*, *Trichophyton*, and *Epidermophyton* genera (Gladwin & Trattler, 2011).

As we develop new interventions, control mechanisms need to combat specific pathogens, their upstream factors, *and* their interactions with each other. Only by accepting that illness stems from a collection of external agents and pathogens can society further 1) prevent disease, 2) promote health, and 3) prolong life.

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