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Developing Infectious Disease Strategies for the Developing World
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1. INTRODUCTION

New infectious diseases continue to emerge and old ones have re-emerged in recent decades. Often these events begin and take root in developing countries. Infectious diseases of the developing world or emerging infections are defined by the Institute of Medicine as an infectious disease that has come to medical attention within the past two decades, or for which there is a potential that its prevalence will increase in the near future. Frequently, these diseases exist in nature as zoonoses and cross over to humans when people come into contact with formerly isolated animal population, such as monkeys in a rain forest that become less isolated with deforestation. Drug resistant organisms may also be considered as emerging infections since they result from human influence. Human immunodeficiency virus (HIV), Ebola virus, hantavirus pulmonary syndrome, monkey pox and multidrug-resistant Mycobacterium tuberculosis (MDR-TB), Severe Acute Respiratory Syndrome (SARS) associated coronavirus and avian influenza are examples of emerging infections. Many of these infections have arisen and become major health issues in the developing world, in part due to selection factors as noted above. Additionally, inadequate resource for public health surveillance and treatment of these illnesses plus poor sanitation and nutritional status may contribute to their flourishing. Once established, these illnesses then pose concerns for all mankind as we have truly become a global community. For these same reasons even common infections such as rotavirus gastrointestinal infection or respiratory syncytial virus (RSV) exert a greater
toll in the developing world. Thus, even as molecular biology advances approaches to diagnoses, new challenges to prevention and treatment of infectious diseases continue to emerge. Through a discussion of avian influenza and MDR-TB, primarily, we will demonstrate the magnitude of the problems of infectious diseases in the developing world and discuss approaches that can be taken to in an attempt to monitor and contain these new threats as they emerge.

2. AVIAN INFLUENZA

Throughout history influenza has been a major infectious disease problem for man causing significant morbidity and mortality. Influenza viruses are members of the Orthomyxoviridae (myxo = mucous, Gr.) family and are classified into three types A, B, and C, based on the composition of their viral nuclear proteins. Influenza A viruses are further categorized into subtypes based on the antigenic structure of the two-surface membrane glycoproteins, hemagglutinin (H) and neuraminidase (N). Both of these proteins play critical roles in the viral life cycle. The hemagglutinin protein is involved in the process of viral attachment and entry to the host epithelial cell to initiate the process of viral infection. The neuraminidase is involved at the other end of the replication cycle as it functions to snip the cell membrane releasing newly made viral particles from the infected cell.

There are 15 distinct hemagglutinins (H1–H15) and nine neuraminidase subtypes (N1–N9) that have been described in nature. Until recently, human influenza viruses only contained H1, H2, H3 and N1 or N2 subtypes. Avian influenza viruses may have additional combinations of the 15 hemagglutinin and 9 neuraminidase proteins.

The influenza virus genome is composed of 8 segmented pieces of RNA with each coding for a separate viral protein. These viral proteins may change slowly (antigenic drift) through point mutations occurring during viral replication or suddenly (antigenic shift). The latter occurs only in influenza A strains and it results from a combination of the segmented genome described above and the ability of influenza A strains of human and avian origin to co-infect the same host (typically, pigs or swines are most receptive), and share their genetic information. During this process of reassortment a new strain acquiring one of the avian surface protein genes (H or N) may emerge. Such a novel strain then eludes pre-existing immunity in people previously infected with influenza and may spread rapidly among the entire population. This defines the potential for worldwide spread or an influenza pandemic. A number of influenza pandemics were documented over the 20th century with the most notable being the 1918–1919 Spanish or swine flu epidemic. During this pandemic, a new for the time H1NI strain arose leading to an estimated 20 million deaths worldwide. Scientists to this date, continue to study this strain attempting to discern virulence factors that contributed to the severity of illness caused by this strain. It has been suggested that the recently observed avian influenza H5N1 strain to be described below may share some of these same virulence properties which may contribute to the > 50% mortality observed in the limited number of human cases reported to date [1]. Specifically, this virus predominately attaches to lower respiratory tract cells (type II pneumocytes, alveolar macrophages and nonciliated bronchiolar cells) leading to
severe lower respiratory tract damage. However, it does not appear to attach well to upper respiratory tract cells, possibly explaining the low human-to-human risk from this strain [2].

The crowding of people, swine, and bird species in areas of the developing world such as Southeast Asia creates an environment that favors the origin of such strains. Public health vigilance has contributed to prompt recognition of new strains as they emerge and has contributed to control of their spread through destruction of bird and/or swine populations.

The H5N1 avian influenza that has attracted so much attention over the last several years does NOT presently meet the criteria of an antigenically shifted strain. It is presently an avian strain that has not undergone reassortment with a human strain and is not well adapted to humans. Only a small number of people (n = 204, with 113 deaths) have been confirmed as infected to date, and the vast majority of these individuals apparently acquired the virus through close contact with infected birds and/or consuming undercooked infected bird products [1,3]. Still the increasing geographic spread of infected birds beyond Asia to Africa and Europe, the transmission to felids (tigers and leopards) through consumption of raw infected chickens in Thailand, and the spread of reported human cases from Thailand and Viet Nam in 2004 to Cambodia, China and Indonesia in 2005 and Azerbaijan, Egypt, Iraq, and Turkey in 2006, raises concerns for a potential pandemic should further adaptation to humans occur.

2.1. Neuraminidase inhibitors

In the event of such a pandemic should arise, where do we stand in treating and preventing the spread of this virus? Since human influenza A (H5N1) isolates are resistant to the M2 inhibitors amantadine and rimantadine, these antivirals do not have a role for the treatment or prophylaxis against this strain. The neuraminidase inhibitors oseltamivir, 1, and zanamivir, 2, have in vitro activities against the human H5N1 isolates; however, recent data suggest that higher doses for longer periods (7–10 days vs. the prior recommendation of five days) may be required to be effective [4]. Oseltamivir is an oral agent approved for prophylaxis and treatment of influenza infections. Zanamivir is delivered topically to the respiratory tract with similar indications.

Oseltamivir resistance in human isolates from Viet Nam has been noted [5,6]. These strains may not be resistant to zanamivir [6]. Stockpiles of drug will be needed for prophylaxis and treatment if they are to be used in the event of a new pandemic.
A long-acting neuraminidase inhibitor, peramivir, 3, has begun Phase I clinical trial to begin to determine whether it may be an intravenous option for this disease [7].

2.2. Avian influenza vaccine

Traditionally, vaccination has been the principal approach to protecting individuals against influenza. Currently, no influenza A H5N1 vaccine is available although several candidate vaccines are being developed. Preliminary data suggest that either higher concentrations of antigens than used in seasonal influenza vaccines and/or addition of adjuvants to these vaccines will be necessary to induce protective responses [8]. Gearing production, to rapidly make necessary quantities, of such a vaccine in the event of pandemic spread will be a great challenge to the vaccine industry.

Thus, although great progress has been made in understanding the biology of avian influenza H5N1 and although the virus is not presently capable of efficient human-to-human transmission there is reason for concern as noted above. Continued surveillance in animal and human populations and infection control measures to limit its spread are critical, while we learn to better combat this virus (or some other future strain) with pandemic potential.

3. MDR-TB

In 1952, when Selman Waksman received the Nobel Prize for his discovery of streptomycin, the first effective tuberculosis drug, he proclaimed that the conquest of the “Great White Plague”, which was previously incurable and associated with up to 50% mortality, was in sight. Five decades later, tuberculosis remains a global epidemic and currently affects 2 billion people, or 1/3 of the world’s population, killing 2 million of them annually. The World Health Organization (WHO) reports that new infections are increasing by 1% per year. By 2020, WHO predicts there will be 1 billion new infections, 200 million of who will develop active disease, and 35 million deaths caused by tuberculosis [9].

Tuberculosis is a particularly frustrating disease to cure because of a multitude of confounding factors. In fact, one of the greatest ironies is that the majority of antibiotics used to treat tuberculosis are still very effective. However, successful
treatment requires a combination of multiple drugs for at least six months. The majority (95%) of tuberculosis occurs in the developing world, where the high relative cost, poor accessibility of medications, and weak health infrastructure causes poor compliance and subsequent selection of resistant strains of *M. tuberculosis* to the drugs it was exposed to. Two-thirds of people with TB do not have access to effective therapy. But even when therapy is available and properly utilized, it may be incompletely effective against these multi-drug resistant strains of tuberculosis. A Beijing/W genotype strain, which has developed resistance to both first and second line TB drugs, is of particular concern. A recent review combining > 29,000 patients in 49 studies from 35 countries has found it to be epidemic in Cuba, the former Soviet Union, and South Africa, and endemic in East Asia [10]. And, estimates place the cost of treating MDR-TB at $250,000–$750,000 per patient, because of the extra isolation, monitoring, medical supervision, and medication costs required.

Hence, there has been renewed interest in developing new drugs for the treatment of tuberculosis. Current goals include compounds which can successfully treat active tuberculosis in a shorter period of time and/or with less frequent, intermittent dosing; compounds to deal with MDR-TB; and compounds to prevent tuberculosis in people at risk of MDR-TB. In fact, a recent Cochrane review covering appropriate studies to address the problem of treating latent tuberculosis infection in people exposed to MDR-TB found there were no randomized controlled trials in the database that have assessed the effectiveness of treatment [11].

There is also a need for relatively inexpensive drugs and medicines that can be given safely with antiretroviral (ARV) medications for HIV, because of the growing problem of tuberculosis and HIV co-infection. One-third of the 39 million people infected with HIV, are also infected with TB, mostly in sub-Saharan Africa. AIDS patients are particularly vulnerable to TB because of their weakened immune systems, which makes them more susceptible to contracting TB or allows previous infection with TB that has been suppressed and contained by the immune system to become active. TB is a leading cause of death for people living with HIV/AIDS, but treating both diseases simultaneously is difficult. Many of the first-line TB medications like rifampin cause adverse drug–drug reactions if given with ARV medications, because both utilize the same hepatic metabolic pathway.

Although more than 40 years has passed since the last novel TB drug, rifampin, was discovered, there are a large number of new drugs now in the pipeline. Many are still in early preclinical stages, but this discussion will focus on those already in clinical human trials and of particular relevance to the developing world.

### 3.1. Quinolones

#### 3.1.1. Moxifloxacin

Moxifloxacin, 4, is a methoxyfluoroquinolone which is already available and approved for the treatment of acute respiratory infections such as community-acquired pneumonia, intra-abdominal infections, acute sinusitis, and skin infections. It is an inhibitor of DNA gyrase, which is an enzyme important in bacterial growth and
replication. It has an excellent safety profile and has already been used by 42 million patients worldwide. However, the drug has not been adequately evaluated in children and pregnant or lactating women.

*In vitro* and *in vivo* studies have demonstrated good activity against *M. tuberculosis* [12,13]. Moxifloxacin has a minimum inhibitory concentration (MIC) against *M. tuberculosis* fourfold lower than levofloxacin, a second-generation fluoroquinolone already in use for MDR-TB. (Older fluoroquinolones like levofloxacin and ofloxacin are only used for MDR-TB treatment because of initial studies showing lack of superiority to existing first-line drugs.) It also has a long half-life and high area under the curve concentration. A murine model study found that substituting moxifloxacin for isoniazid decreased the overall time necessary for TB eradication by two months. Moxifloxacin is currently in four different Phase II trials in eight countries – Brazil, Canada, South Africa, Spain, Tanzania, Uganda, the United States, and Zambia, with a goal of demonstrating efficacy as a first-line component of a shorter, standardized TB treatment regimen. The hypothesis is that moxifloxacin substitution for isoniazid or ethambutol in the usual four drug standard regimen (isoniazid, rifampin, ethambutol, and pyrazinamide) during the first two months of treatment will significantly increase the proportion of patients with culture-negative sputum at 8 weeks, compared with the standard regimen. Phase II trials, are expected to complete in 2007, with Phase III trials to follow. Moxifloxacin metabolism also does not utilize the hepatic cytochrome P-450 system, and does not lead to adverse reactions when taken alongside ARVs. However, one recent study in Italy found that 12/38 patients treated with long-term moxifloxacin for TB developed adverse reactions. None of the reactions was irreversible or fatal, and moxifloxacin was felt to be safe and result in treatment success in 31/38 patients. The success rate was only 5/14 in MDR-TB patients [14].

3.1.2. Gatifloxacin

Gatifloxacin, 5, is another methoxyfluoroquinolone that is actually furthest along in clinical development for tuberculosis treatment. Like moxifloxacin, it is used to treat a variety of bacterial infections, has been used globally for many years, and has no interactions with ARV drugs. Gatifloxacin is a structurally similar to moxifloxacin and likely to have the same mechanism of action against bacterial DNA gyrase. This means cross-resistance is possible between these two drugs. Gatifloxacin’s toxicity and drug–drug interaction profile is similar to moxifloxacin’s.
Early clinical studies in Brazil have shown gatifloxacin to possess equivalent anti-
tuberculosis activity to moxifloxacin and similar, but slightly less potent, activity to
isoniazid [15]. One murine study suggests that gatifloxacin in combination with
ethionamide or pyrazinamide, could be an alternative regimen to cure active TB.
This would be important in treating patients with drug-resistant tuberculosis where
the standard isoniazid/rifampin-containing regimen would be ineffective [16].

A large multicenter phase III clinical trial is currently enrolling a planned 2000
patients in South Africa, Senegal, Kenya, Benin, and Guinea to evaluate whether
using gatifloxacin instead of ethambutol can shorten the standard TB treatment in
adults to four months. This study began in 2005, and is to be completed in 2009 [17].

3.1.3. TMC207

An additional quinolone derivative, TMC207, 6, (formerly known as R207910) is
currently being studied in Phase II trials in patients with tuberculosis. It is a di-
arylquinolone, with activity against both sensitive and MDR strains of TB. In a
murine model it appeared equivalent to both isoniazid and rifampin at lower doses,
and superior to the combination of isoniazid, rifampin, and pyrazinamide bacte-
ricidal activity by at least 1 log unit when combined at a higher dose with any two of
the three. It even appeared to be superior to the combination as monotherapy. In
combination with isoniazid or rifampin, TMC207 decrease TB sterilization time
from four to less than two months. Its activity appears to be directed against
mycobacterial ATP synthase, giving it a unique mechanism of action, compared
with other tuberculosis drugs, including fluoroquinolones like moxifloxacin. More-
over, the half-life was greater than 24 hours, suggesting once weekly dosing is
possible [18].

\[ \text{Structure of TMC207} \]

3.2. Nitroimidazoles

3.2.1. PA-824

PA-824, 7, is a nitroimidazopyran discovered in 1995 as a potential cancer drug. In
2000, a study revealed its potency against \textit{M. tuberculosis} [19]. It has a novel
mechanism of action inhibiting protein and lipid synthesis, which is effective against
both TB and tested clinical isolates of MDR-TB. It attacks the mycobacteria in
both the initial, intensive phase of TB therapy, as well as the later, continuation phase. In the intensive phase, PA-824 has bactericidal activity comparable to isoniazid, and in the continuation phase, its bactericidal activity is close to the combination of isoniazid and rifampin. PA-824 also has activity against both actively replicating and the static, slow growing mycobacteria. This has the potential for shortening the course of therapy, since many current drugs are only active against actively replicating mycobacteria, and \textit{M. tuberculosis} spends weeks to months in its static, slow-growing phase. In a murine model, PA-824 was more potent than rifampin when used in combination with moxifloxacin and pyrazinamide, and that when all four drugs were used together, the duration of treatment could be reduced to 3 months or less [20]. PA-824 successfully completed a phase I clinical trial in the U.S. in August 2005, and a phase II trial is planned for later in 2006, ending in 2008.

PA-824 has a bioavailability of about 40% and single oral dose rapidly travel to important target sites like the lung and spleen. PA-824 also does not inhibit the hepatic cytochrome P-450 isoenzyme system, suggesting it could be safely used with ARVs [21]. There is no evidence of genotoxicity, by such standard tests as Ames. The Global Alliance for TB Drug Development, a non-profit, public-private partnership has directed and funded PA-824’s development and has obtained exclusive worldwide rights to PA-824 and its derivatives, so that the technology will be available royalty free in endemic countries.

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\subsection{3.2.2. \textit{OPC-67683}}

Work has also begun on second-generation nitroimidazoles. In Japan, a nitroimidazo-oxazole \textit{OPC-67683}, 8, has entered phase I clinical trials and a backup nitroimidazo–oxazole is in early development. Preclinical data has been encouraging so far [22]. Second-generation nitroimidazopyran analogs with greater \textit{in vivo} potency in animal models have also been identified.

\subsection{3.3. Pyrroles}

\subsubsection{3.3.1. \textit{Sudoterb (LL3858, LL4858)}}

Sudoterb belongs to a class of compounds known as pyrroles, which are plant alkaloids. Sudoterb has been reported to have potent anti-TB activity \textit{in vitro} and
in vivo. In vitro, sudoterb has bactericidal activity similar to isoniazid and is synergistic with rifampin. The combination of sudoterb with isoniazid, rifampin, and pyrazinamide led to complete sterilization of both sensitive and MDR-TB strains in mice within two months, and in combination with rifampin and pyrazinamide, cured TB in all animals after three months. Sudoterb exhibits good oral bioavailability with once daily dosing. Phase I studies began in India in 2005 [23]. The structure of sudoterb has not been released.

3.4. Tuberculosis vaccine

Currently, BCG (Bacille Calmette-Guérin) is the only licensed tuberculosis vaccine. It has a number of shortcomings, among which is a relatively short period of protection, and poor antibody stimulation response beyond childhood. Since there are clearly many problems with treating TB at this point, a lot of effort and money has been focused on creation of a vaccine, as a means of preventing future infections in those at highest risk and putting a cap on the ever increasing TB epidemic.

Unfortunately, it appears the obstacles in the development of such a vaccine are no less challenging than those hindering drug development. It is well know that BCG varies in effectiveness among those who receive it. This has previously been attributed to different environmental factors or differences in the BCG strains used to create the vaccine. However, a recent gene analysis has found that *M. tuberculosis* is genetically distinct in different parts of the world and has evolved into 6 different lineages: East-African-Indian, East-Asian, Euro-American, Indo-Oceanic, and two West-African. These strains appear to have adapted over time to specific human populations, which suggest separate, wholly different vaccines might be required for each region [24].

Those who receive an effective vaccine may still not develop adequate protection. BCG is known to stimulate Th1 immune cells, which leads to the development of protective antibody and drives *M. tuberculosis* into latency in the body. In many areas of the developing world, parasitic helminthic infections are extremely common. Parasites stimulate a Th2 immune cell response, usually associated with an allergic response. This increase in background Th2 response is antagonistic to the Th1 cell response, and, in theory, will blunt or lead to an inadequate immune, as well as cause impaired bactericidal activity [25].

Nevertheless, work continues on a vaccine. A leading candidate, MVA85A, utilizes a recombinant vaccinia virus Ankara (MVA) expressing antigen 85A. MVA85A completed a Phase I clinical trial in the United Kingdom in 2004. When given with BCG, Th1 levels were up to 30-fold higher than groups given MVA85A or BCG alone [26]. Further clinical trials in the United Kingdom and Gambia are in progress. Another vaccine, Mtb72F/AS02A consisting of a recombinant fusion protein (Mtb72F) formulated in a proprietary adjuvant system (AS02A) has shown promising results in preclinical studies to induce strong, long lasting cellular and humoral immune responses. In addition, the vaccine has shown a good safety and immunogenicity profile in Phase I trials. Phase II trials are planned to being shortly [27]. Even with concerns with the potential efficacy of a vaccine, there may still be a
role for its use. Combining the use of a vaccine with antituberculosis drugs seems to augment the bactericidal activity of the drugs, particularly with regard to the slow-growing mycobacteria [21].

We are still years away from actually seeing any of these developments in tuberculosis treatment actually enter clinical practice. But if their full potential is achieved, then it is likely that none of the current first-line drugs will be part of the new, optimized regimen, which should finally begin to decrease both the incidence of tuberculosis, and the development of MDR-TB.

4. CONCLUSION

It is clear that although drug and vaccine development for both avian influenza and MDR-TB is well underway, there is so much more that needs to be done. Currently, it is the developing world which is most affected by both of these infections; yet, the drugs and vaccines are not being optimized for these areas. Drug regimens need to be shorter and simpler, not only to make them affordable to the population at risk but also to prevent the development of drug resistance. Vaccines of more widespread efficacy are also needed to protect as well as prevent these infections from becoming global epidemics. Hopefully, this review has demonstrated the impact for all mankind of emerging infections in the developing world and will stimulate ongoing development of approaches aimed at addressing these issues for the people affected, and for the entire world.

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