SUPPLEMENT ARTICLE

Why Infectious Diseases

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Infectious diseases is a broad discipline that is almost unique in contemporary medicine with its ability to cure and prevent disease, to identify specific disease causes (microbes), and to deal with diverse, sometimes massive outbreaks. The value of the infectious disease practitioner is now magnified by the crisis of antibiotic resistance, the expanding consequences of international travel, the introduction of completely new pathogen diagnostics, and healthcare reform with emphasis on infection prevention and cost in dollars and lives. Infectious disease careers have great personal rewards to the practitioner based on these observations. It is unfortunate that we have been so effective in our work, but relatively ineffective in convincing the healthcare system of this value.

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Students of medicine have multiple career options with various attractions and concerns. So it is with the discipline of infectious diseases. As with all medical specialties, infectious diseases has unique features that are important to highlight: Among medical specialties, this one is consistently changing, often unpredictable, usually exciting, and incredibly rewarding for health impact. It is also often challenging and seemingly underappreciated, at least until needed. These facts appear to be relatively idiosyncratic to this discipline with a menu of priority pathogens that is in constant flux and weaponry that will change in unpredictable ways. The extraordinary kinetics and ability to intervene successfully using public health, preventive vaccines, and disease-limiting antimicrobials are its great strengths. The following are some of the highlights and unique features of a career in the science and practice of infectious diseases. The menu includes the litany of epidemics, heroic efforts to conquer disease, our expectations with antimicrobials, vaccines and public health, and challenges that may lead to transformative interventions.

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The field of infectious diseases is kinetic, unpredictable, and layered with surprises that sometime require heroic efforts from a diverse field of scientists and practitioners.

- On 2 October 2001, a patient with fever and confusion was seen at a Florida medical center by Dr Larry Bush, an infectious disease physician. He examined the cerebrospinal fluid, saw boxcar gram-positive rods, diagnosed anthrax, and predicted bioterrorism [1]. This was strong stuff at a time no one had thought much of bioterrorism anywhere in decades and especially in an obscure, small town in Florida. The ensuing epidemiologic investigation showed anthrax spores in this patient's workplace, the local postal service, and a letter received by the patient. This was the index case of the anthrax bioterrorism epidemic that shook the country in 2001.The result was a major national preparedness response to not only bioterrorism, but also preparedness for natural disasters, epidemics, and other major public health threats.
- In 1977, Dr Alan Steere, a rheumatologist from Yale School of Medicine, led an investigation of an outbreak of arthritis involving 39 children and 12 adults in Connecticut. Most of the patients had asymmetric swelling and pain of large joints, especially knees, and some also had an erythematous, annular rash [2]. It was initially called "Lyme arthritis," but most physicians thought it was simply juvenile rheumatoid arthritis. Dr Steere was convinced it was an infection and moreover, that it was arthopod-born based on

epidemiology and clinical features. His relentless pursuit of the pathogen was finally rewarded with the discovery of the newly recognized spirochete in the blood and in typical skin lesions [3]. The specific agent was subsequently defined in a another extraordinary effort, this time by Dr Willie Bergdorfer, who had spent much of his career studying the microbiology of the hindgut of ticks; he successfully isolated the pathogen that he considered his last and most important scientific project [4, 5]. That agent is named in his honor: *Borrelia burgdorferi* [6].

- Dr Robin Warren, a pathologist in Australia, made the historic discovery that gastric biopsies from patients with gastritis showed a large burden of curved bacteria. No one paid attention until a young gastroenterologist, Dr Barry Marshall, agreed to study the association. This pairing was considered an "odd couple"; Dr Warren was described as quiet, thoughtful, and persistent whereas Dr Marshall was self-described as brash and determined [7]. Subsequent studies consistently showed the association between this curved microbe with gastritis and peptic ulcer disease, but there was almost uniform opposition from both gastroenterologists and infectious disease physicians. Larry Altman, noted medical editor for *The New York Times*, wrote that never in his experience had he witnessed such fierce opposition from the medical community to the possibility that peptic ulcer disease was caused by a microbe (L. Altman, personal communication, 16 May 2012) [8]. This prompted 2 proponents, Drs Barry Marshall and Alan Morris, to perform the ultimate experiment—they swallowed a flask of *Helicobacter pylori* (and suffered from the experience; L. Altman, personal communication, 16 May 2012) [9]. The long-term result of this unrelenting battle is now well known: *H. pylori* is accepted as the cause of peptic ulcer disease and its sequela, guidelines for diagnostic testing and treatment are based on *H. pylori* as the pathogen, this agent is listed as a class 1 carcinogen, and Nobel prizes were awarded to Drs Warren and Marshall [10].
- In early September 2012, Dr April Pettit, an infectious disease physician in Tennessee, saw a patient with *Aspergillus* meningitis following an epidural steroid injection [11]. This prompted her to notify Dr Marion Kainer at the Tennessee Health Department, who then set up shop with a sleeping cot in the health department to facilitate a nonstop investigation [12]. This was the beginning of the infamous national epidemic of *Exserohilum rostratum* meningitis associated with the contaminated steroids that led to 741 cases and 55 deaths in 18 states. Credit here is to Dr Pettit for recognition and prompt notification, to Dr Kainer for her aggressive response on behalf of the victims, and to the Centers for Disease Control and Prevention (CDC) for the hasty intervention. (Somewhat disappointing is the fact that compounding pharmacies are still unregulated.)
- In 1981, Dr Anthony Fauci read the 3 July edition of *Morbidity and Mortality Weekly Report* [13] describing gay men with Kaposi sarcoma or *Pneumocystis carinii* pneumonia in California. For the first time in his life, Dr Fauci had what he called "chill pimples" ("chill bumps"), and this led to a career change to find the cause, treatment, and prevention of AIDS. This must be now viewed as possibly the most remarkably successful attack on an important infectious disease since Fleming discovered penicillin.
- In February 2003, severe acute respiratory syndrome (SARS) was a newly described, severe disease in humans that was often fatal and appeared to travel by air routes, but had no established pathogen or treatment. Dr Klaus Stohr at the World Health Organization (WHO) identified the finest virology laboratories in the world and asked them to collaborate to define the pathogen with the condition that all information would be shared on the Internet and there was no ownership of the data. The 11 participating labs with varying skills were spread throughout the world, so the daily conference calls started with "Good morning, good afternoon, and good evening." The etiologic agent was described in an unauthored "Global Alert" on 16 April 2003 and in *The Lancet* with "Multicentre Collaborative Network" as the authors (see [14]). This unselfish collaboration under strong leadership is credited with the rapid solving of a global crisis that eventually showed 8000 cases with 774 deaths in 25 countries.
- These anecdotal experiences (bioterrorism, Lyme disease, peptic ulcer disease, iatrogenic fungal meningitis, human immunodeficiency virus [HIV]/AIDS, and SARS) illustrate the unpredictable challenges and some of the unique responses that have left a major imprint on medicine. It is noteworthy that all started with strong leadership and came to closure with either elimination or successful management.

EPIDEMICS

Epidemics of infections are predictable to occur, but largely unpredictable in time, place, microbe, and consequences. The following highlights some of the recent epidemic records and surprises in this category:

- West Nile Virus was first reported in New York City in 1999 and reached a 10-year zenith for reported cases in 2012 with 5674 cases, including 51% with the dreaded neuroinvasive form of the disease [15].
- Coccidioidomycosis: The total number of reported cases increased 10-fold in 13 years, from 2265 in 1998 to 22 401 in 2011 [16].
- Malaria reported in US travelers reached a record high of 1925 cases in 2011 [17].
- Chikungunya virus reached a record number of cases in the Caribbean with >1000 reported cases, including 10 in US travelers to St Martin [18]. This pathogen is highlighted because

global warming is expected to make it endemic in the southern United States and because of its substantial morbidity with possible long-standing arthritic complications [19].

- Measles: The largest number of annual reported cases in the United States in 17 years was noted during 2011–2013. It now appears that 2014 will be worse [20]. Measles was declared eradicated in 2000 but has now become a problem, primarily in those refusing vaccination, but also in some with documented vaccination [21]. Measles continues to be an important infectious disease challenge due, in part, to the extraordinary public health issues that cost one health system $800 000 to deal with the potential epidemiologic consequences of a single case [22].
- Pertussis: This infection is resurgent in the United States and Europe, with increased cases including epidemics in children and adults and involving both vaccinated and unvaccinated individuals [23]. This is thought to reflect waning immunity to the acellular vaccine and the need for a new vaccine [24].
- Meningitis: 2013–2014 reporting showed 4 outbreaks of *Neisseria meningitidis* meningitis, 2 on college campuses and 2 among gay men in New York City and Los Angeles [25].
- Influenza: This is a continual concern based on the ever-present threat of pandemics with devastating consequences (1918–1919, 1957–1958, 1968–1969, 1977–1978, 2009–2010) that seem difficult to predict or control [26, 27]. Limitations of current expertise were illustrated with influenza A(H1N1) swine flu, as the standard concept based on historic precedent is that new influenza epidemics come from Asia in the wintertime, but this one came in the eastern hemisphere in the summertime [27]. The more recent threats that could pose serious consequences are influenza A(H7N9) and influenza A(H5N1) [28–30]. Both show high mortality rates, but little evidence so far of that single critical mutation permitting attachment to the hemagglutinin antigen to permit sustained person-to-person transmission [26].
- Middle East respiratory syndrome (MERS) coronavirus: This coronavirus is a major global concern with analogies to the SARS coronavirus in terms of its perceived potential to become a global epidemic with high mortality and no apparent treatment [31, 32]. Of immediate importance in the United States is recognition of risk with appropriate diagnostic testing, isolation, and management of persons with severe, unexplained pneumonia associated with recent travel to the Arabian Peninsula (MERS) [32].
- Foodborne disease: Widespread foodborne epidemics are now a common consequence of the massive food distribution system that permits contaminated beef or lettuce from Mexico to reach stomachs in distant multistate areas, with medical consequences involving hundreds or thousands of people. This includes the more recent emergence of the GII.4 Sydney strain of norovirus. These outbreaks seem likely to continue, with unpredictable pathogens in unpredictable places [33–35].
- Heartland virus: A recently encountered tick-borne disease in Tennessee and Missouri with 10 cases and 2 deaths [36].
- Polio-like virus infection with extremity paralysis has been recently reported in 5 and possibly 25 children in California [37].
- Ebola virus: WHO has reported an outbreak in Guinea involving a new clade of this usually fatal infection [38].

This listing could continue almost indefinitely. The point is that epidemics are the domain of infectious diseases and public health, with the expectation for management or prevention of outbreaks with requirements for detection, reporting, isolation, and case management. The listing here includes diverse pathogens, some life-threatening diseases, infections with important public health implications, an upsurge of pediatric infections in adults, many travel-related infections, multiple public health threats, and the continuous concerns for influenza and foodborne disease.

INFECTIOUS DISEASE INTERVENTIONS

The major weaponry of the infectious disease catalog includes antibiotics, vaccines, and public health. These categories are remedial reading, but some facets are worthy of emphasis.

Antibiotics

The value of antibiotics seems obvious. The first patient to receive penicillin was a young woman with β-hemolytic streptococcal bacteremia with fever of 39.4°C–41.2°C daily for 4 weeks. She received penicillin intravenously starting 14 March 1942, promptly recovered, and survived to age 90 years [39]. This would appear to be "evidence-based medicine" with an n = 1. The following statement from Dr Walsh McDermott in 1982 summarizes this breakthrough especially well: "Penicillin gave more curative power to a barefoot, itinerant care provider in the deepest reaches of Africa than the collective powers of all physicians in New York City" [40]. The more recent experience with bacterial resistance and sparse pipeline threatens this miracle, but antiviral development is quite different, primarily for HIV and hepatitis C virus (HCV). It now appears that patients with HIV can achieve near-normal longevity [41]. HCV infection is even more impressive in terms of speed of progress and ability to cure. The HCV treatment story reflects the efficiency of basic science to define targets, pharmaceutical skills of industry, well-organized trial networks, and a regulatory agency (US Food and Drug Administration [FDA]) that facilitated product development [42].

Vaccines

The impact of vaccines is also impressive. A comparison of annual incidence of vaccine–preventable diseases in the United States reported for the period prior to availability of the designated vaccine compared with its incidence in 2013 shows the

decrease in polio as 100%; diphtheria, 100%; rubella, 99.9%; mumps, 99.6%; invasive type B *Haemophilus influenzae*, 99.2%; and pertussis, a disappointing 88%. A recent report concluded that the global total for lives saved by vaccines exceeds 100 million [43]. The impact could be substantially greater with more global access, fewer refusals, and a better pertussis vaccine.

Infection Control

A recent CDC analysis of annual costs associated with 5 major nosocomial infections totaled $9.2 billion per year in the United States with the following rank order by median cost/case: central line bacteremia, $45 814; ventilator-associated pneumonia, $40 144; surgical site infection, $20 785; *Clostridium difficile* infection, $11 285; and catheter-associated urinary tract infection, $896. This illustrates the challenge and the priorities [44]. Another challenge is epidemics involving nosocomial pathogens, as shown with the *Klebsiella pneumoniae* carbapenemase-producing bacteria (KPC) in the National Institutes of Health (NIH) Clinical Center. This began with a patient transferred from a New York City hospital with a KPC infection and became the source of an institutional outbreak that required extraordinary efforts to control, including a wall constructed to isolate cases, removal of plumbing (as a possible source), use of matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) molecular diagnostics to detect cases and carriers, hydrogen peroxide room aerosols, and "whole house" surveillance cultures. The epidemic was finally halted, but the toll was 18 cases and 6 fatalities over 6 months [45,46]. Another KPC epidemiologic investigation showed widespread distribution of this microbe from a long-term acute-care facility in the Chicago area [47], and others have demonstrated distribution of KPC by air travel from India to Europe [48]. These epidemics require extensive resources and specialized skills; they will be expected to increase substantially in the era of "bad bugs."

KINETICS OF INFECTIOUS DISEASES

There is no specialty field in medicine that demonstrates shifting priorities like infectious diseases. To illustrate this point, I have summarized the "Hot Topics" discussed in the "What's Hot in Infectious Diseases" presentation to the annual meeting of the American College of Physicians in 2004, compared with the presentation in 2014, to illustrate the nearly complete change of priorities in a relatively short time.

2004

Avian influenza, rabies (first survival without vaccine), West Nile virus, bioterrorism, transfusion-associated Jacob-Creutzfeldt disease, USA300 strain of methicillin-resistant *Staphylococcus aureus* (MRSA), SARS, and *Chlamydia pneumoniae* and its role in coronary artery disease and influenza.

2014

Carbapenemase-producing gram-negative bacilli, colistin, constant infusion of β-lactam antibiotics, molecular diagnostics, a litany of epidemics, new pathogens (*Mimivirus*, *Borrelia miyamotoi, Emmonsia* species, and *Bradyrhizobium enterica*), *C. difficile* gene sequencing, the microbiome, and HCV.

Note that the 10-year interval resulted in a completely new agenda for what was considered timely and important in the field based on rapid changes in topical microbes, new epidemics, and new diagnostics, (but not new antimicrobials). It is impossible to predict the menu for 2024.

CHALLENGES AND OPPORTUNITIES

Resistance

It is now known that genes for resistance to antimicrobial agents were well established in bacteria at least 3 million years before evidence of human life [49]. The use of antibiotics has selected for these genes by Mendelian laws, making it increasingly difficult to control previously treatable infections. This problem was predicted by the father of antibiotics, Alexander Fleming, who, in 1945, wrote that ". . . the public will demand the drug and . . . then will begin an era . . . of abuses. The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to another individual and perhaps from there to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save. In such a case, the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to an infection with penicillin-resistant organisms. I hope this evil can be averted" [50]. Also of note is the prediction by Nobel Laureate Joshua Lederberg: "The future of humanity and microbes will likely evolve as . . . episodes of our wits vs their genes" [51]. It now appears that Fleming's prediction is a harsh reality and evolutionary microbial resistance genes are gaining the upper hand, reflecting the combination of massive antibiotic use and lack of new pharmacologic agents. The result is the alarming escalation of antibiotic resistance that is global and applies to nearly all categories of treatable pathogens, leading some to predict "the postantibiotic era." This resistance has been declared a "crisis" by the Infectious Diseases Society of America, the CDC, WHO, the US Congress, and the US President.

A disturbing observation in the United States is the conspicuous absence of a national plan to deal with resistance, including the lack of a living record of antibiotic consumption and resistance correlated by location and trajectory. This is in sharp contrast to the European Union, which includes 28 countries with 24 official languages and diverse cultures, but has systematically collected data on antibiotic consumption and microbial resistance patterns for 15 years [52,53]. This has resulted

in multiple publications with data reviews, studies of interventions, messages to consumers such as an eBug Internet program for students, a European Antibiotic Awareness Day, standardized methods to collect data [54] and a recent 12-point plan with budget to address the issue [55]. Their data are striking in showing the dramatic association between per capita antibiotic use and national resistance patterns. For example, antibiotic consumption in Greece is nearly 4 times that of the Netherlands, so we expect more resistance problems in Greece, but the magnitude of this difference is alarming: Bacteremic carbapenemase strains among all bacteremic *K. pneumoniae* isolates appear to be about 150 times more common in Greece, and MRSA as a percentage of all *S aureus* isolates is about 40 times higher [51]. The European Union appears to have a mature and substantive model to learn from, with the important caveat that it functions well because there is no claimed ownership, as there are 28 equal partners.

There are also some good national programs that have successfully addressed specific problems to learn from:

- EU data for 2002 showed that France had embarrassingly high antibiotic use rates, accompanied by increasing resistance by *S. pneumoniae*. This prompted a national campaign targeting prescribers and consumers on antibiotic abuse and its consequences. The goal was a 25% reduction in antibiotic prescriptions for the entire country; they achieved a 26% reduced resistance [56] and also achieved the largest decrease in per capita antibiotic consumption for any nation in the history of the global antibiotic fund [57].
- A recent report from Israel showed a national campaign to reduce the incidence of KPC. Analysis of their results with a prevention bundle showed a reduction from 55 per 100 000 patient-days to 4.6 per 100 000 patient-days [58].
- The United Kingdom addressed the issue of the epidemic NAP-1 strain of *C. difficile* through gene sequencing and aggressive antibiotic control. The result was a national 61% reduction in *C. difficile* infection rates [59].

The 3 examples given are based on national data addressing major challenges with impressive results. In the United States, this remains a unanswered challenge, but is also an opportunity for the skills of the infectious disease discipline in terms of data collection, evaluation, interventional trials, and policy implementation into practice, primarily in the form of antibiotic stewardship.

Gene Sequencing to Inform Infection Control

Recent reports using gene sequencing suggest that conventional methods of infection control could substantially improve this effort. Examples: (1) Results from the United Kingdom have largely disproven conventional teaching regarding the epidemiology of *C. difficile* infection [59]; (2) this technology also appears to contradict some contemporary concepts about transmission patterns of *S. aureus* [60]; and (3) it has proven to be a valuable tool in outbreak investigation of KPC infections in a hospital [45] and in a large community outbreak of KPC involving multiple facilities [47]. It seems clear that as this technology gets faster and cheaper, it will be embraced as an infection control standard [61], although there needs to be caution and skill in interpreting results [62].

International Infectious Diseases

This work in developing countries is another attractive career option based on need, probability of impact, and unique special programs such as the President's Emergency Plan for AIDS Relief, the Bill & Melinda Gates Foundation, and others. Some of this is direct patient care, but possibly very attractive targets for impact are the development and implementation of innovative programs that deal with the vast need combined with minimal resources [63].

Healthcare Reform

The new healthcare system should value infectious disease expertise based on its important role in addressing resistance and costs associated with nosocomial infections. Nevertheless, it is feared that the current structure and payment system are not constructed as a good fit to prioritize infectious disease skills. Specifically, there is no code for preventing infections, conserving antibiotic use, or preventing resistant pathogens. This might be an erroneous conclusion, or the situation may change as the system matures and becomes serious about addressing the crisis. "Bundles" to deal with healthcare efficiencies are in vogue and could be a strength of infectious diseases. An example is the 5-step central line bacteremia prevention bundle that proved effective in trials [64]. Generalized adoption of this bundle was predicted to save 18 000 lives and $1.8 billion per year in US hospitals [65], and subsequent actions by clinicians, regulatory agencies, and stakeholders have resulted in an estimated 63% decline in central line bacteremia rates [66].

THE FUTURE

- Stewardship: Solving or reducing the problem of antibiotic resistance largely depends on antibiotic development and reducing antibiotic abuse. The major on-site forces for improving smart antibiotic use at the point of care are antibiotic stewards—preferably infectious disease or pharmacy personnel trained in this skill to improve the speed of detecting resistant or epidemic pathogens. The tools are obvious to infectious diseases–trained clinicians, but often require methods that are not well inculcated into hospital or clinic practice. Methodology with proven value for antibiotic conservation include short-course regimens (virtually always wins or ties in trials), use of

procalcitonin to facilitate decisions on when to start or stop antibiotics, use of molecular diagnostics to improve pathogen-targeted antibiotic decisions, outpatient infusion therapy to reduce inpatient risk (and cost), optimal use of the agents we have, waiting room with notices that the doctor will prescribe antibiotics only according to guidelines, acknowledgement of possible microbiome harm, and possible use of social network media [52, 53]. Nevertheless, there must be caution: The new US healthcare system represents socialized medicine largely managed by capitalists, which invites both quality and chicanery. For example, the Centers for Medicare and Medicaid Services' "6-hour rule" for treating community-acquired pneumonia had improved outcome advantages, but also led to overprescribing, declined use of diagnostics, perceived antibiotic abuse, and increases in *C. difficile* infections. Given the priority of cost containment and its relevance to infectious diseases, infectious disease training should probably include attention to the business of medicine.

- Molecular microbial diagnostics: These are rapidly being developed and introduced into clinical use for detection of epidemic pathogens or resistance genes with advantages of speed, precision, and sensitivity. Most polymerase chain reaction (PCR)–based tests define a specific pathogen with extraordinary sensitivity within 60 minutes. The FDA has approved these PCR tests to detect at least 14 viruses and 10 bacteria [67]. These tests may also be useful for early detection of epidemic pathogen or resistance genes [68]. It seems clear that the introduction of molecular tests for general use may be difficult to interpret in the context of clinical care, so these new tests will require a substantial stewardship from the infectious disease community. This was illustrated in a trial to guide antibiotic decisions based on results of a PCR-based diagnostic to detect MRSA in purulent soft tissue infections that had no significant impact on antibiotic selection [69]. Gene sequencing will be a new and important role for the infectious diseases–trained clinician as it becomes more readily available for defining transmission patterns to inform infection control practice.
- Microbiome: Study of the microbiome at various anatomical sites represents a major NIH-sponsored initiative that could possibly translate into important opportunities to treat or prevent multiple conditions [70, 71]. This work is at the dawn of development, but the early reads suggest a potential role in obesity, allergies, autoimmune disease, cancer, diabetes, heart disease, and other conditions [71, 72]. It is also apparent that antibiotics have a profound and long-lasting impact on the microbiome [71]. This field requires a transformation in our conventional understanding of infectious diseases, as the "pathogens" are communities of microbes that communicate in contrast to the Koch postulate of "one microbe, one infection." An example is a recent report showing that volunteers fed steak and eggs (lecithin) have conversion by gut flora to trimethylamine-*N*-oxide, which is a marker of atherosclerosis [72]. This microbial interaction could be altered with antibiotics. The long-term goal is to define associations and intervene possibly with antibiotics and probiotics; this work may also illustrate potential harm to redefine risk-benefit ratios for antibiotics.
- Bundles: Another potentially important role for infectious diseases–trained clinicians is the development of bundles that prevent infectious disease complications. An example is central line bacteremia, as described above [64–66]. That experience can now be applied to multiple iatrogenic infection risks associated with specific patients or procedures, possibly prioritizing those with the greatest healthcare consequences as described above. The role of infectious diseases is to define the bundle, design the study, and then implement them when results are convincing or even mandated.

CONCLUSIONS

Specialized skills in the management and study of infectious diseases are an increasingly important specialty in contemporary medicine. The roles of practitioners in the discipline are diverse, usually important, and sometimes critical, but commonly undervalued by contemporary priorities in healthcare systems and healthcare reform. It would be difficult to find another discipline in medicine that has such extraordinary diversity, surprises, value in patient care, and clinical relevance for both domestic and international applications. For many trained in medicine, joining the field of infectious diseases is simply the right thing to do.

Notes

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