

Case Study



Infectious Lifesciences Laboratory

Hypothetical Bioscience Facility for Case Studies¹

International Biological Threat Reduction Department

Sandia National Laboratories

Albuquerque, NM USA

www.biosecurity.sandia.gov

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Sandia is a multiprogram laboratory operated by Sandia Corporation, a Lockheed Martin Company, for the United States Department of Energy's National Nuclear Security Administration under contract DE-AC04-94AL85000.

Background: Republic of Prowazekii

Population

The population of Republic of Prowazekii is 246,821,286 with a density of 134 persons per km². The society is heterogeneous with 14 different ethnic groups. A recent survey identified 87% of the population as Muslim, 7% Protestant, 3% Catholic, 1.7% Hindu, 0.7% Buddhist, 0.1% Confucian, and 0.5% “other”. Many languages are spoken throughout the country, but English is the official working language.

The Mallie Misanthropes group is a large southern island of the country and is seeking to secede from the Republic. This is an increasingly active political movement with strong support in the southern province. A small, more radical subgroup of Mallie Misanthropes uses periodic acts of “terrorism” to draw political attention to its struggle for independence.

Infectious Diseases

In general, the incidence of infectious diseases in the Republic of Prowazekii has decreased over the past two decades. Influenza is the most frequent disease of public health concern followed by food-borne illnesses. The large majority of these food-borne infections are attributed to diarrhea from Rotavirus and *Escherichia coli*. Other human infectious diseases of import include viral hepatitis A and typhoid fever which have incidences of 117 and 810 per 100,000, respectively. The country is also experiencing a reemergence of tuberculosis. There are many highly infectious, potentially zoonotic diseases endemic throughout the country, including *Bacillus anthracis*, *Yersinia pestis*, *Brucella* sp. and rabies virus. Outbreaks in the agricultural industry are common. This has the potential to become a significant public health concern because of the large population who works in the agriculture industry and has close contact with livestock. The Republic of Prowazekii is officially free of Foot-and-Mouth Disease and Rinderpest, but has almost annual outbreaks of avian influenza and Newcastle Disease. The country also experiences occasional outbreaks of Vesticular Stomatitis.

Biotechnology/Bioscience Regulations

Several years ago, the Republic of Prowazekii’s government identified bioscience as an area of potential high growth for the country, and is especially interested in promoting agricultural and health applications of biotechnology. There are few national regulations in this field. Agricultural Ministerial decree No. 1745 established procedures for commercializing genetically modified crops. The Republic of Prowazekii lacks import and export regulations of any type, but a government committee is currently considering legislation and guidance. Republic of Prowazekii is party to the Biological and Toxins Weapons Convention (BWC). A 1982 law implemented the BWC agreement, including prohibiting and criminalizing possession or use of biological weapons.

Currently, laboratories may follow the World Health Organization’s *Laboratory Biosafety Manual* (LBM) for guidance on laboratory biosafety. In response to growing concerns domestically and internationally, the country passed biosecurity regulations last year. The Biosecurity Act classifies biological agents into four categories, each with separate protocols and penalties.

Importantly, the new law also requires that agents in from Low-Very High Risk (see following page) be handled with appropriate biosafety controls. Facilities with any Low-High Risk biological agents must implement a risk-based approach to both laboratory biosafety and biosecurity. Additionally, records must be kept of all activities involving Very High Risk, High Risk, or Medium Risk agents. Agents that are not specifically listed in the regulations are not currently controlled. The government is permitted to inspect facilities to ensure that appropriate controls and record keeping are in place.

Risk	Agents	Summary of Regulations
<p>Very High Risk</p> <p>agents of extreme risk</p>	<ul style="list-style-type: none"> • Foot and Mouth Disease Virus • Lassa Virus • Japanese Encephalitis Virus (Flaviviridae) • Dengue Virus (serotypes 1-4) • Variola Major Virus • Crimean-Congo Hemorrhagic Fever 	<ul style="list-style-type: none"> • Possession, import, export, and domestic transfer of Very High Risk agents are categorically prohibited, except when specially designated by the Minister of Health or the Minister of Agriculture. • Appropriate biosafety controls must be used • Facilities must implement a risk-based approach to both laboratory biosafety and biosecurity • Records must be kept of all activities involving Very High Risk agents
<p>High Risk</p> <p>high risk agents</p>	<ul style="list-style-type: none"> • Bacillus anthracis • Bovine Spongiform Encephalopathy (BSE) • Clostridium botulinum (botulinum toxin) • Francisella tularensis • Highly Pathogenic Avian Influenza (H5N1) • Severe Acute Respiratory Syndrome (SARS) Corona Virus • Yersinia pestis • Multi-drug resistant Salmonella enterica (serotype typhi) 	<ul style="list-style-type: none"> • Prior permission from the Ministry of Health or Ministry of Agriculture must be obtained in order to possess or transfer Group 3 agents. • Appropriate biosafety controls must be used • Facilities must implement a risk-based approach to both laboratory biosafety and biosecurity • Records must be kept of all activities involving High Risk agents
<p>Medium Risk</p> <p>agents are not considered high risk, but still have a significant potential for malicious use</p>	<ul style="list-style-type: none"> • Herpes B Virus • Brucella spp. • Burkholderia mallei • Burkholderia pseudomallei • Coxiella burnetti • Eastern Equine Encephalitis Virus • Exotic New Castle Disease Virus • Hantaan or other Hanta viruses • Hendra Virus • Tick-borne Encephalitis Viruses • Nipah Virus • Monkeypox Virus • Multi-drug resistant Mycobacterium tuberculosis • Rabies Virus • Rickettsia rickettsii • Rift Valley Fever Virus • Vesticular Stomatitis Virus 	<ul style="list-style-type: none"> • Activities involving Medium Risk agents do not require prior permission, but identification or possession must be reported to the Ministry of Health or Ministry of Agriculture within seven days. • Appropriate biosafety controls must be used • Facilities must implement a risk-based approach to both laboratory biosafety and biosecurity • Records must be kept of all activities involving Medium Risk agents
<p>Low Risk</p> <p>agents are not considered a sufficient risk to require reporting of possession and transfer, but do merit some caution</p>	<ul style="list-style-type: none"> • Chlamydia psittaci • Cryptosporidium parvum • Mycobacterium tuberculosis • Shigella dysenteriae (serotype 1) 	<ul style="list-style-type: none"> • Any accidents with Low Risk agents must be reported. • Appropriate biosafety controls must be used • Facilities must implement a risk-based approach to both laboratory biosafety and biosecurity

Rickettsia National University

Overview

Rickettsia National University (RNU), home to the Infectious Lifesciences Laboratory (ILL), is located in Typhusville City, is one of the leading universities in the Republic of Prowazekii. RNU employs 300 people and has 18,500 students from across the Republic of Prowazekii and 25 countries. There are seven graduate and professional schools, including: College of Veterinary Medicine, College of Medicine, College of Engineering, College of Arts and Sciences, College of International Relations, the Teacher's College, and the Business College.

Campus Security

Campus security is maintained through a combination of guards provided by the ministry, and through additional guards that RNU hired themselves. Campus security reports to the Director of RNU for work, but their time sheets go to the ministry for approval. Disciplinary action or replacing personnel by RNU requires ministry approval.

The total workforce for campus security personnel is 12 officers, led by one Commanding Officer. Campus security primarily walk the perimeter of the campus and respond to incidents after staff on campus has alerted them to a theft or attempted break-in. Campus security works in three shifts: 08.00 – 15.00, 15.00-24.00, and 24.00 – 08.00, 2 officers for each shift. Campus security officers are equipped with the following:

- A straight baton,
- A small flashlight,
- A handheld radio, and
- Keys to all buildings, doors, and gates.

When one security officer is not patrolling the perimeter, the other is stationed in the control station. It is approximately a 5-minute drive, 7-minute bike ride, or 20-minute walk from the campus police control station to the Biosciences Quad.

Threats of Concern to Campus Police

A radical extremist groups sympathetic to the animal rights movement called Freedom for Furrries was founded in 1983. It has been active in the Republic of Prowazekii, and occasionally in Typhusville. The group appears to have two goals: 1) the liberation of captive animals and 2) the destruction of capital necessary to conduct such research. However, the Band of Mercy's website instructs its followers to "take all necessary precautions against harming any animal, human and non-human."

In the past few years, activists against genetically modified organisms (GMOs) have become active in Typhusville. Although they have not damaged property yet, similar groups in neighboring countries have targeted facilities that conduct research on GMOs, **particularly** newly constructed biotechnology laboratories.

Last year, one graduate student in chemistry was arrested on charges of manufacturing the synthetic drug methamphetamine in a RNU laboratory. There were also some thefts of property, including computers and laptops from the main laboratories within RNU. The researchers whose labs were broken into lost all their data as a result of the theft.

RNU Memorandums of Understandings (MOUs)

The University has established Memorandums of Understandings between RNU and the city police force, the fire department, and emergency medical services. Responders are told to contact the Director of RNU for access to the facility during an emergency. The MOU was established 5 years ago, and has not been amended or updated.

Emergency Services

The RNU has an agreement with the local hospital ambulance service in the event of a spill. Typhusville City Police Department: 5km from RNU. With sirens on, this drive can take anywhere from 15 minutes to 70 minutes depending on traffic, weather, and the time of day.

Access to Campus Buildings

The University has an open campus; there is no controlled perimeter. All classroom and research buildings are unlocked from 6 am – 8 pm Monday through Friday. Buildings are locked outside of these hours.

For a given laboratory building, one master key opens the exterior doors and a second master key opens all laboratories. Thus, all students, technicians, faculty, and custodial staff working in a particular building have the same key. Keys are handed out by the facilities building representative. A student receives a key to the laboratory building if a faculty member completes a Key Authorization Form for that individual.

Bioscience Quad

The Bioscience Quad is the central focal point for all of RNU's bioscience and biomedical programs. The medical school, teaching hospital and clinic, veterinary school, animal hospital and clinic, and the biosciences department all reside on this quad. The teaching hospital and the animal hospital each house several small clinical laboratories. The main biosciences department building is principally classrooms, faculty offices, and some laboratories (for non-infectious studies). All of the department's work with infectious substances is currently conducted in the Infectious Lifesciences Laboratory. The Quad also has a centralized shipping and receiving facility.

RNU Infectious Lifesciences Laboratory (ILL)

Facilities

ILL currently has four laboratories in which it conducts a variety of research and analysis. The ILL has a Microbiology section, Zoonosis section, Toxicology, and Enteric Pathogens. The Laboratory has one facility with engineering controls and standard operating procedures that match a biosafety level 3 laboratory, and the rest are equal to a biosafety level 2 laboratory. The BSL3 has one pass-through autoclave, and there are several small autoclaves in individual labs.

Currently, ILL does limited animal research in the form of confirmatory diagnostic testing in rodents and vaccine challenges in poultry, but the facility primarily relies upon tissue culture.

ILL Staff

There are 40 staff (researchers, technicians, and students) currently working at the ILL. Faculty, research technicians, graduate students, undergraduate students have access to the laboratories, although undergraduate students are not allowed in the BSL3 laboratory. Housekeeping, facility staff, and the biorisk officer have access to all aspects of the laboratory.

Current Research Efforts Underway at ILL

Aspergillus flavus

The Biosciences Department at Rickettsia National University were provided with a grant from the Fungal Research Trust and NIAID to work with characterization of *A. flavus* strains. Current work utilizes fluorescent aptamers and flow cytometry to identify toxic and potent hepatocarcinogenic aflatoxins that *A. flavus* produces.

Bacillus anthracis

PCR-based detection methods are being developed for use in identifying virulence genes specific to *B. anthracis* to facilitate the identification of *B. anthracis* from other closely related species. Faculty in the Biosciences Department and Medical School are collaborating to study the use of anthrax toxin as cancer chemotherapy.

Botulinum toxin

Researchers at the Medical School of Rickettsia National University are working on intrapyloric injection of botulinum toxin A for treatment of gastroparesis. The project is looking at both long-term and short-term outcomes in response to this new medical therapy.

Candida albicans

The Biosciences Department is currently using carbon nanotubes and *Candida albicans* to produce electrically conductive and stable bio-composite materials that can be utilized as temperature sensing elements. Efforts are being aimed at engineering durable and low-cost sensors for use in civil engineering projects.

Dengue Virus

More rapid, sensitive, and serotype specific diagnostic tests are being developed for more accurate detection of different Dengue infections. Further, work on serotype specific and tetravalent vaccines for Dengue is being pursued. The new ILL facility will host the research and development teams focused on these aims.

Fusarium moniliforme

Scientists in the Biosciences Department are developing antifungal botanicals that are more specific for *F. moniliforme* with fewer side effects for the crops that they are administered to. The research aims to solve current problems that the Republic of Prowazekii faces in rice production as there has been an increase in infection of *F. moniliforme* strains that affect human and animal health.

H5N1 Avian Influenza

Research on H5N1 at RNU has been limited to providing assistance to the Ministry of Agriculture in the testing of clinical samples. Positive samples have been sent to the closest World Health Organization Influenza Collaborating Center for confirmation. Pending completion of the new ILL Containment Laboratory Complex, the faculty propose to study the efficacy of oseltamivir therapy in ferrets.

Japanese Encephalitis Virus

Scientists at Biosciences Department are trying to better understand the causative agent of Japanese encephalitis virus as it is closely related to the West Nile Virus. Greater understanding can lead to results in tackling both viral pathogens that plague the Republic of Prowazekii.

***Mycobacterium tuberculosis* and MDR-TB**

Researchers seek to develop tools for improved diagnostics of *M. tuberculosis* and monitoring disease progression of drug-resistant tuberculosis. Efforts are aimed at developing immunological reagents for early diagnosis and disease monitoring. Current projects utilize green fluorescent proteins.

Rabies Virus

Researchers are studying how the rabies virus crosses the blood-brain barrier, where it is most lethal. The team is also exploring why the T and B effector cells of the immune system do not cross the barrier, and thus cannot clear the infection.

***Salmonella enterica* (serotype typhi)**

Researchers are investigating the distribution of drug resistance in *S. typhi* across the Republic of Prowazekii. Clinics from throughout the country send isolates to the ILL Enteric Pathogens Group. The Group is testing the isolates for susceptibility to ciprofloxacin, chloramphenicol, and tetracycline. This is a long-term study to examine the change in distribution of drug resistant strains that began a decade ago.

***Shigella dysenteriae* serotype 1**

There is no vaccine available for *Shigella* spp., and only limited treatment options for infection with antibiotic resistant strains. ILL researchers are conducting preliminary research that will aid the development of an attenuated strain suitable for use as a vaccine.

Yersinia pestis

Researchers at Rickettsia National University are currently working on immunization efficacy studies. Whereas live attenuated vaccines are highly reactogenic and not licensed for use in humans, inactive whole cell vaccines that are less reactogenic provides poor protection against pneumonic plague and immunization that require multiple doses. The College of Veterinary Medicine and Medical School are working together to develop a vaccine that is less reactogenic but still provides immunity with fewer doses.

Agents in Repository Collection at ILL

The ILL maintains a reference collection of agents for varying purposes. The Principle Investigators believe the following to be currently in their repository, but cannot confirm definitively:

Acinetobacter calcoaceticus

Adtinobacillus lignieresii

Aspergillus flavus

Aspergillus fumigatus

Bacillus anthracis

Bacillus cereus

Bordetella bronchiseptica

Brucella spp.

Campylobacter fetus

Candida albicans

Candida tropicalis

Clostridium botulinum

Clostridium chauvoei

Clostridium novyi

Clostridium septicum

Clostridium tetani

Corynebacterium bovis

Corynebacterium equi

Corynebacterium Pseudotuberculosis

Corynebacterium renale

Erysipelothrix rhusiopathiae

Fusarium moniliforme

Haemophilus paragallinarum

Klebsiella pneumonia

Mycobacterium aurum

Mycobacterium intracelulare

Mycobacterium kansasii

Mycobacterium phlei

Mycobacterium tuberculosis

Mycoplasma gallinaceum

Mycoplasma iners

Pasteurella haemolytica

Pasteurella multocida

Pseudomonas mallei

Pseudomonas pseudomallei

Salmonella spp. (other than typhi)

Salmonella typhi

Staphylococcus aureus

Staphylococcus equi

Staphylococcus hyicus

Staphylococcus pneumonia

Staphylococcus pyogenes

Other Departments at RNU

College of Veterinary Medicine

The College of Veterinary Medicine employs approximately 75 faculty and 195 staff. There are 220 students in the doctor of veterinary medicine program, a four-year veterinary medical curriculum of classroom and laboratory instruction and clinical rotations in the University Hospital for Animals. The College also has a graduate program (MS and PhD). Graduate fields of study within the College include comparative biomedical sciences, microbiology, immunology, pharmacology, physiology, biochemistry and cellular and molecular biology, and zoology. A core group of veterinary faculty has a newly expanded emphasis on bacterial pathogenesis and post-genomics research against microbes.

College of Medicine

There are approximately 525 medical students, 500 interns and residents, and approximately 200 graduate students and post-doc fellows studying medicine at RNU. The College of Medicine has 25 academic departments, 19 clinical and 6 basic sciences, as well as the Unit for Laboratory Animal Medicine and Department of Medical Education. In addition to their work in research and education, faculty in clinical departments provide inpatient and outpatient care at the University Hospital and Out Patient Clinic.

Biosciences Department

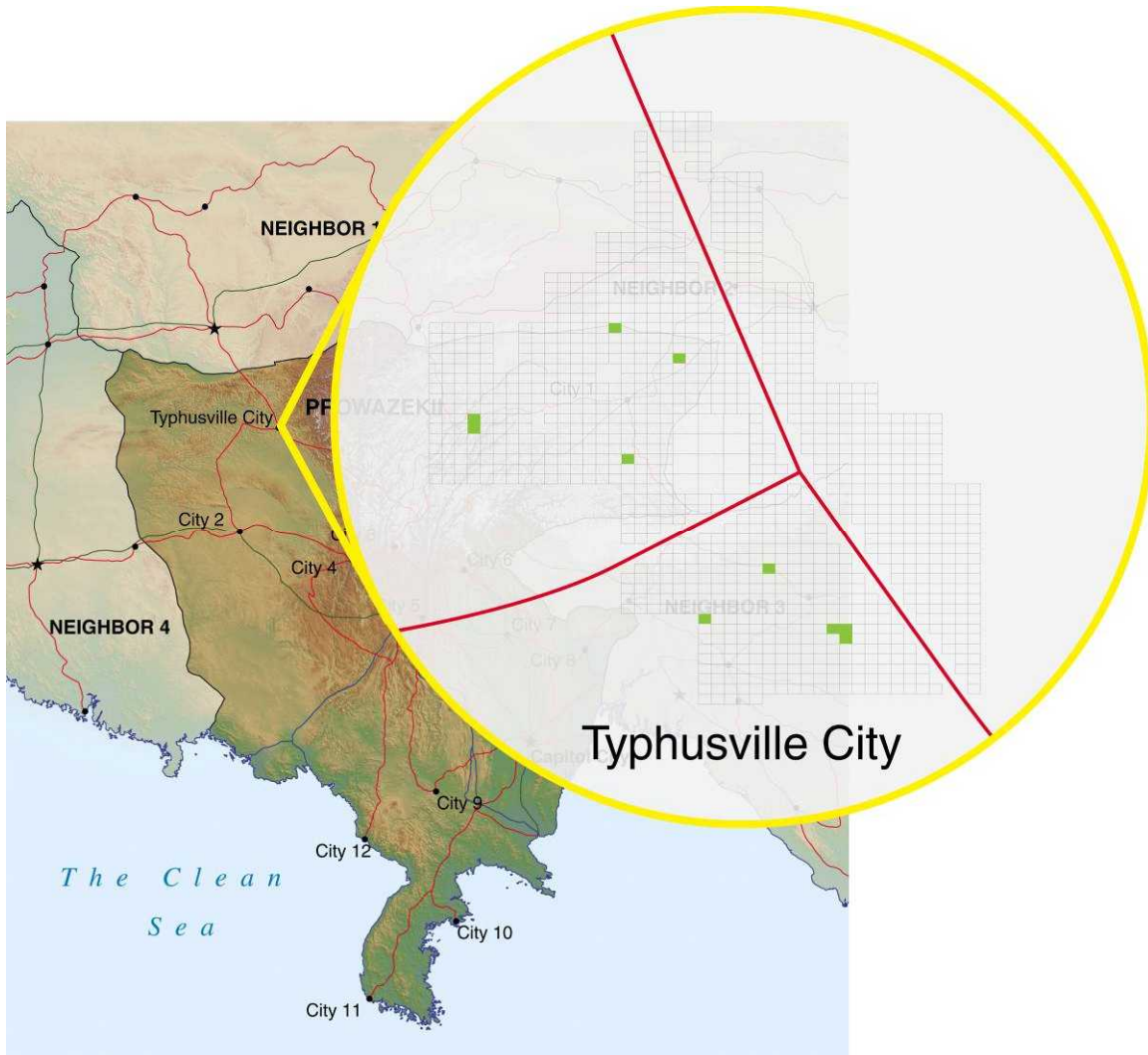
The Biosciences Department resides in the College of Arts and Sciences. With 41 tenured and research faculty, 66 professional staff, 75 graduate students, and 125 undergraduate students, the Department is a dynamic research and teaching environment. Facilities for cell biology, genomics, immunology, environmental microbiology, and molecular biology include the capacity for small animal studies. Large animal research is done in partnership with the College of Veterinary Medicine. The cornerstone of RNU's biosciences research program is the Infectious Lifesciences Laboratory (ILL). ILL is the country's premier bioscience research and educational institution. The laboratory primarily focuses on zoonotic emerging infectious diseases, since these are the source of almost all emerging diseases throughout the world. ILL's mission is to conduct research and development of new vaccines, drugs, and diagnostics for these emerging diseases.

Maps

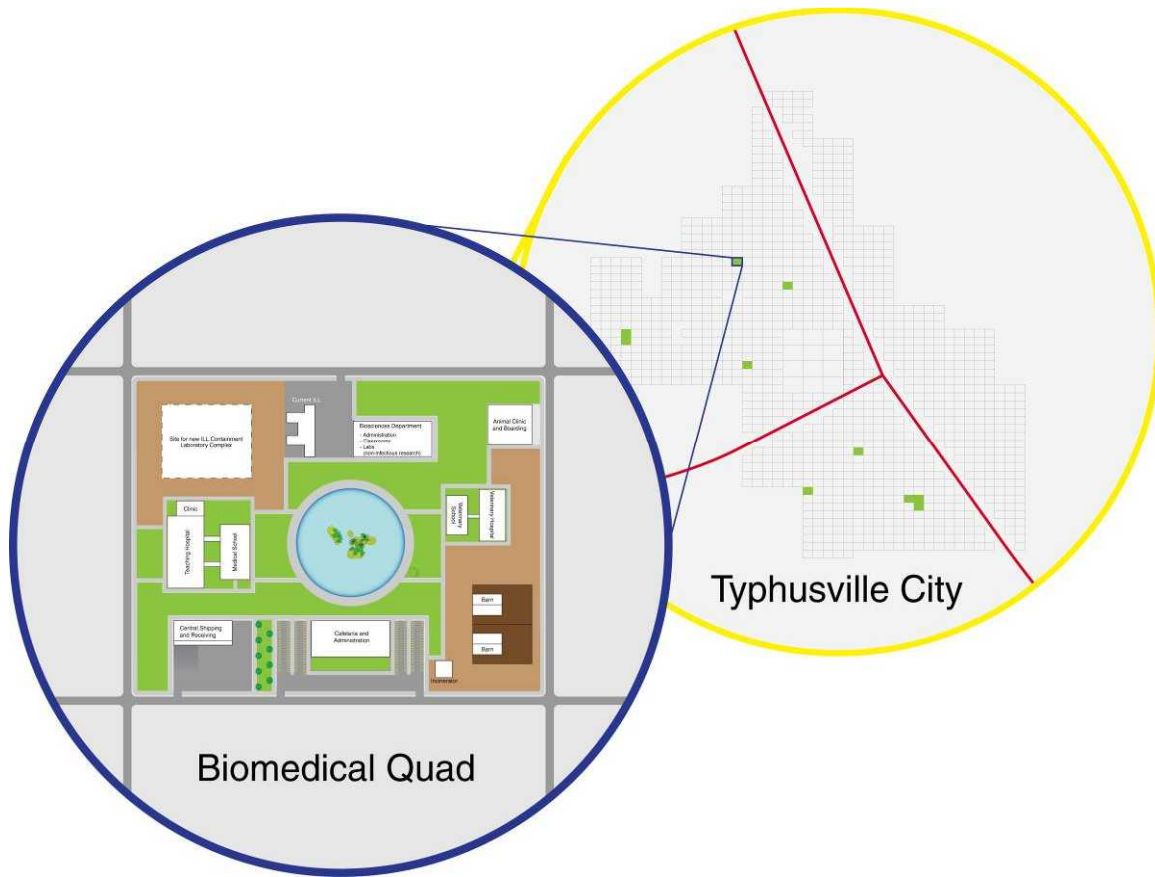
Republic of Prowazekii Map

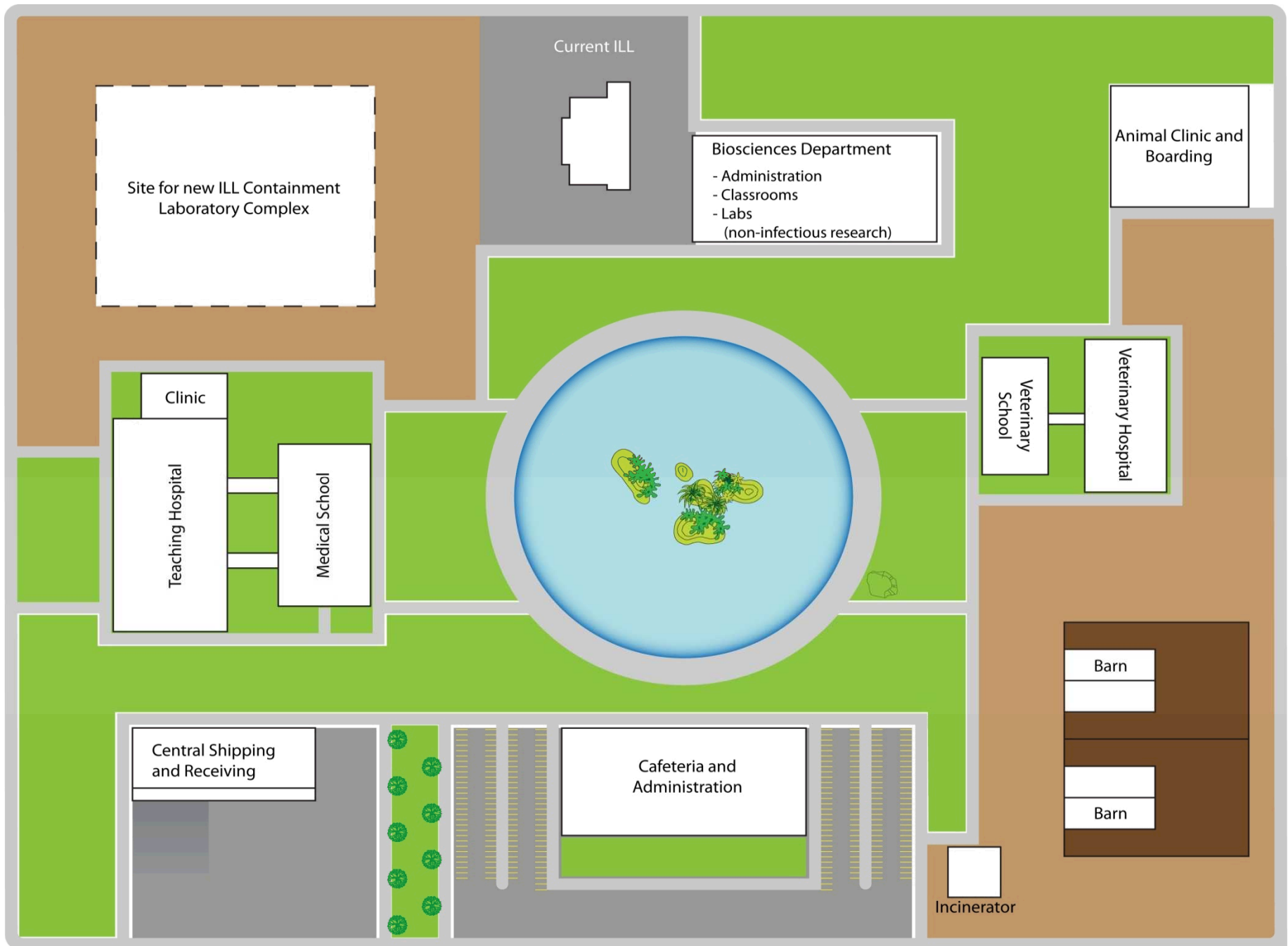


Typhusville City Map



Map of RNU's Biosciences Quad







ILL Facility

ility Callouts

BSL II)

r

emergency exit

BSL II)

Area entrance

uilding entrance

and work areas

y entrance / West emergency exit 1

emergency exit 2

area

closet

restroom

's restroom

ave access area

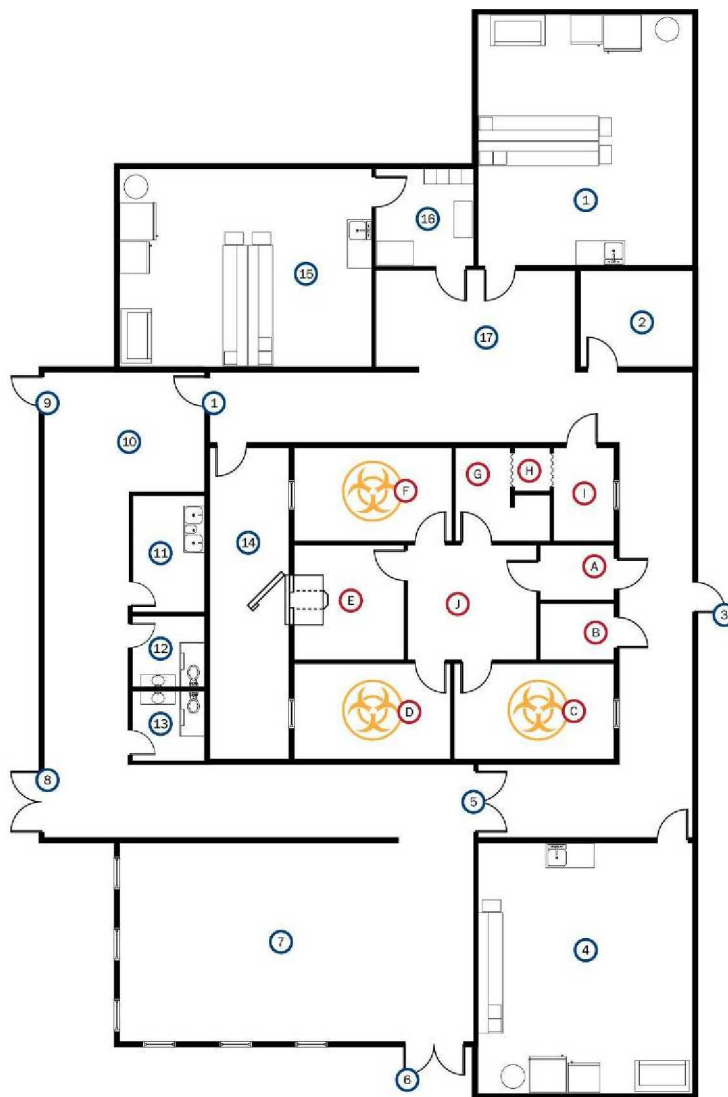
BSL II)

ng room

om

Lab 1 (BSL III) Callouts

- A. Airlock
- B. Mechanical room
- C. Lab 1a
- D. Lab 1b
- E. Autoclave
- F. Lab 1c
- G. Change room
- H. Shower
- I. Entry
- J. Central area



Case Study Reference: Descriptions of Adversaries

Insiders

These individuals have authorized access. A facility may have only one type of insider (the Insider with Full Access) or a facility may have multiple types of insiders based on the level of access to the agent that might be stolen, such as Insider with Full Access, Insider with Building Access, and Insider with Site Access. There are some attributes that are assumed to apply to all Insider adversaries. An Insider's motive may be due to disgruntlement, psychological imbalance, personal gain (in collusion), or the desire to commit a terrorist act. The malevolent insider would be expected to abort any theft attempt in order to avoid detection because, with authorized access, the insider can wait for a more opportune time to steal the agent. In general, the insider is an employee who has become malevolent, and is not assumed to have paramilitary training.

The Insider with Full Access may be a laboratory worker or other individual who has unescorted access to the asset. Authorized access affords this person extensive knowledge of the facility and operating systems. It also provides this adversary with opportunity. Insiders with Full Access to biological materials are usually scientists and technicians who have a high level of technical training and sophistication. Thus, they often have all of the means at their disposal to successfully acquire and maliciously disseminate a biological agent.

Outsiders

These individuals do not have authorized access to the site. Information specific to the site and vicinity should be used to modify these notional descriptions or create additional ones.

Terrorist Group: The motive of this adversary is to cause mass casualties, an economic crisis, or widespread fear and/or it may seek to make a political statement. This adversary is assumed to be well-funded, and may be supported by a state, religious group, individuals, or even organized crime. Being well-funded, the Terrorist Group is also well-equipped and trained, and able to rehearse an attack. The Terrorist Group is highly organized. The Terrorist Group is violent and willing to die. The Terrorist Group also has access to, and the skill to utilize, significant explosives and arms. As an Outsider, the Terrorist Group does not have access or specific opportunity.

Single Terrorist: This adversary may be motivated to make a political statement, to express anger, to steal an agent in order to ultimately achieve personal goals, or to commit an act of bioterrorism. This adversary has less means than the Terrorist Group, but is still well-equipped and trained, and able to rehearse. He may still be capable of killing or injuring a number of guards or other individuals. The Single Terrorist has the tools necessary to overcome most

access control systems. The Single Terrorist is willing to use violence and force. As an Outsider, the Single Terrorist does not have access or specific opportunity.

Extremist Group: This adversary is motivated to make a political statement or protest against programs for ecological, political, economic, or other reasons. As a result, its objective may not be theft of a biological agent; instead, it may be to destroy property or release animals. However, this group's acts may inadvertently cause an escape of pathogens into the environment by releasing contaminated animals. The Extremist Group has the ability to commit sabotage, and may possess hand tools, items for arson and other facility sabotage, and possibly handguns. The Extremist Group has general information about the facility, but not specific information about the location of the assets or the facility's protection systems. All members of the group are assumed to be Outsiders, thus the Extremist Group does not have access or specific opportunity.

Criminal: This adversary is motivated by financial gain. The Criminal is a single adversary that may have weapons and hand tools. If organized crime is assessed to be a local problem, a Criminal Group adversary can be defined with limited capabilities. The Criminal adversary is also presumed to be an outsider without access or specific opportunity.

Competitive Rival: This adversary seeks to gain competitive market advantage through theft or destruction of proprietary information or experimental materials. The Competitive Rival may include an invited colleague or other visitor who has the intent to steal intellectual property and/or acquire an agent. This adversary is assumed to have limited capabilities, but he may have opportunity with direct, supervised access (i.e., as an Escorted Insider).

Vandal: This adversary may operate individually or in groups. His motivation is to cause a nuisance by damage or destruction. His tools include spray paint, knives, hand tools, and may include guns for target shooters or hunters. A Vandal attacks local facilities is not homicidal. A vandal has no authorized access to the facility or opportunity to steal pathogens and toxins.

Colluding Terrorist Group: This is a combination of an Insider and an Outsider Terrorist Group. However, by involving more individuals, this notional adversary puts themselves at risk of discovery.