Airborne Infection and its Control:

Research at Harvard University from William Firth Wells until the Present.

Edward A. Nardell, MD
Associate Professor of Medicine
Harvard Medical School
Tuberculosis Control Officer
Massachusetts Department of Public Health

Historical Context:

In the 1930's the Massachusetts Department of Public Health engaged William Firth Wells, a sanitary engineer at Harvard, to investigate the possibility that workers in New England textile mills were becoming sick as a result of exposure to bacteria in stagnant water aerosolized to keep down dust[1]. Wells had invented an air centrifuge to sample air for viable bacteria and used it to successfully recover the same bacterial species from factory air that he found in the water used for the aerosol. He had thus shown that respiratory pathogens could spread by the airborne route following aerosolization. His brilliant intellectual leap was to consider the possibility that person-to-person transmission of respiratory infections might also be due to airborne microorganisms[2]. He hypothesized that large droplet aerosols, whether generated artificially in a factory or by the human respiratory tract by coughing or sneezing, evaporated into tiny residua he called droplet nuclei, which were buoyant enough to remain airborne indefinitely under ordinary conditions of room air movement. It would be decades before he and Richard Riley, then a Harvard medical student working with him on the textile mill investigations, would prove that tuberculosis was spread by airborne droplet nuclei[3]. Riley would go on to a brilliant career as a preeminent respiratory physiologist as well as Chairman of the Department of Environmental Health Sciences, Johns Hopkins University, where he continued the work begun by Wells on airborne infection and its control.

Having conceptualized the droplet nuclei mode of transmission, Wells investigated a number of potential environmental control strategies. This was before the discovery of streptomycin in 1946, so effective treatment of tuberculosis, or any other airborne pathogen, was not an option. Wells investigated the use of aerosolized chemical disinfectants, but none of these were satisfactory. He also did both basic experiments and field trials on ultraviolet germicidal irradiation (UVGI) which he found to be both highly effective and practical. In the 30s, Wells demonstrated that upper room UVGI was highly effective in preventing the transmission of measles in suburban Philadelphia day schools[4]. By this time Wells had moved from Harvard to the University of Pennsylvania. However, attempts by others to reproduce Wells' findings in a London school district or in schools in rural upstate New York failed, but an important lesson had been learned[5]. Air disinfection can only be effective if applied at the principle sites of transmission. In the failed clinical trials, measles transmission prevented by UVGI in day schools occurred elsewhere as children interacted in crowded urban tenements in London, or on

school buses in rural upstate New York. Wells' early work stimulated others to study UVGI. Luckiesch published his detailed monograph in 1946, nine years before Wells' own comprehensive work: Airborne Contagion and Air Hygiene, which summarized his most important findings[6,7]. Among Wells' most important research plans was an experimental TB ward, which was carried out in the late 50s and early 60s in Baltimore by his old student, Richard Riley, who was then at Johns Hopkins University.

By the late 50s tuberculosis was widely believed to be spread by droplet nuclei, but there was no scientific proof, nor had the efficacy of UVGI against TB been demonstrated. Wells had envisioned an experimental hospital ward with 6 beds continuously occupied by newly diagnosed patients with infectious TB. Ward air was ducted to a penthouse room above the ward where hundreds of guinea pigs were housed in a special chamber to assure uniform exposure. This was (and remains) the only effective way to sample air for human-source TB. As discussed below, it is possible to use mechanical air sampling for mycobacteria, but only if they are artificially aerosolized in relatively large concentrations. As the Wells-Riley experimental ward would ultimately show, under clinical conditions, viable TB organisms are produced in small numbers and their concentrations in air are so low that
air sample cultures are uniformly overgrown with the much more numerous and faster growing ambient bacteria and fungi.[3,8-10]. Over the 4-year duration of the study, patients on the ward generated an average of only 1.25 infectious doses (droplet nuclei) per day. Presumably, many more particles were produced, but they appeared not to be infectious and were presumed to be dead or dying.

Riley's studies on the experimental ward established with certainty the airborne mode of TB infection, the best estimates of production rates by untreated patients and those started on therapy, the great variability in infectiousness among patients, and the complete efficacy of UVGI in ductwork in rendering air noninfectious. Riley, Middlebrook and Permutt went on to carry out seminal experiments on upper room air disinfection – the UV susceptibility of various organisms, including virulent tuberculosis, and the interaction of room air mixing and upper room UV[11-13]. The last of this basic experimental work was published in 1976[14]. Despite the enormous amount of work generated by Riley and associates and Luckiesch before him, many of the details of applying ultraviolet air disinfection were left unresolved. The rules of thumb currently used to plan upper room UVGI installations are based primarily on Riley's 1976 room studies using BCG as a surrogate organism for TB[15,16]. Newer building designs have much lower ceilings than did the older buildings used for the experimental studies, and the safety and efficacy of available UV fixtures in these settings has never been demonstrated experimentally, or in field trails. For this reason, and despite the fact that the efficacy of other air disinfection strategies has not been scientifically proven either, CDC and US regulatory agencies have been cautious in recommending UV as a primary intervention to prevent TB transmission.[17]

Recent outbreaks:

Research on air disinfection all but ended with the advent of effective therapy for TB and the widespread use of immunization to prevent respiratory viral infections. However, with the resurgence of TB in the US and other developed countries between 1985 and 1992, multidrug resistant (MDR) strains spread within hospitals and other congregate settings, resulting in deaths among patients, prisoners, caregivers and guards, especially among those co-infected with HIV[18]. The result of these outbreaks was a renewed emphasis on TB infection control in congregate settings, including environmental control strategies. Hospitals have reported improved infection control using a combination of administrative and environmental controls, and personal respiratory protection, although the exact contribution of each intervention is not known. Outbreaks are far fewer now that public health interventions have brought case rates in the community under control in resource-rich countries, but institutional transmission is a growing problem in many resource-poor countries, such as Russia and South Africa. Transmission of MDR TB in prisons in Russia threatens TB control in that region of the world, and beyond. While treatment remains the mainstay of TB control, there is a pressing need to revive research on air disinfection, especially methods like upper room ultraviolet air disinfection, which may be useful in preventing transmission in high-prevalence countries. The remainder of this paper reviews current and future research efforts at Harvard School of Public Health and affiliated institutions. Other work on UV air disinfection is being done at Leeds University in the UK, Colorado State University, and in Brazil under the auspices of NIOSH, a branch of the CDC in the US.

Current and Future Research on Ultraviolet Germicidal Irradiation (UVGI):

The research needed to fully exploit the potential of UVGI in reducing TB transmission can be considered as four interdependent strategies, listed in figure I. Each of these research strategies is designed to answer important questions that cannot be answered any other way. In the first two strategies mechanical air sampling is done, but this requires artificial aerosolization of surrogate test organisms in high concentrations in order to avoid long collection periods and overgrowth by the more numerous, rapidly growing bacterial present in air. In the second two experimental strategies, humans are the source of aerosols of human tuberculosis, but mechanical air sampling cannot be used due to low concentrations of airborne TB, and bacterial overgrowth. In the third strategy, large numbers of guinea pigs are used to sample the air from an experimental TB ward, the methodology developed by Wells and Riley more than 40 years ago. The final and ultimate research strategy is a large clinical trial of upper room UVGI in high-risk settings, where humans are tuberculin skin tested as quantitative indicators of TB infection during periods with and without UVGI. Three of the four research efforts are well underway. Only the third strategy, the experimental TB ward, has yet to begin.

The focus of this research is on upper room UV rather than UV air disinfection in ventilation ducts. Although there are good applications for ventilation duct irradiation,

and for portable air disinfection devices that utilize UV in ducts, upper room UV was quickly recognized by Wells, Riley and Luckiesch as potentially far superior under many practical circumstances. While the in-duct approach must rapidly move all room air through relatively small irradiation duct, upper room UVGI uses the entire upper room as an irradiation chamber, depending on convection currents and other slow air motion within the room to deliver infectious air for disinfection. Studies by Lukiesch and by Riley and Permutt have demonstrated high rates of air turnover through the upper room, resulting in rates of air disinfection beyond that achievable by the in-duct approach without unacceptable ventilation noise and drafts. Moreover, disinfecting air in the ventilation duct after it leaves a room will reduce the chance of recirculation, but does little to protect occupants in the room with the source. Finally, many facilities where transmission occurs have little or no mechanical ventilation, especially in resource-poor, high-prevalence countries. The efficacy of UV air disinfection in ventilation ducts can be no greater than the ventilation system. Portable units provide the ventilation as well as the UV, but despite potential noise and drafts, may not produce as many air turnovers in a large room as convection currents and upper room UV. In-duct UV prevents any potential UV exposure of room occupants, but at the low levels of UV permitted in the lower room, health risks are neither a theoretical nor practical concern. UVGI is 254 nm wavelength, highly active against minute airborne organisms, but unable to penetrate the outer dermal layer to cause dermatitis or skin cancer, or reach the lens to cause cataracts, all consequences of exposure to more penetrating, longer wavelength solar UV.

1. **Bench-scale exposure chamber research.** Among the most basic questions that require answers is the susceptibility of various organisms to known doses of UVGI under various conditions. Riley and Middlebrook used a bench-scale exposure chamber to establish the susceptibility of M. tuberculosis as well as BCG and other surrogate bacteria. They found that human TB and BCG were approximately equally susceptible to UVGI, and that E.coli and Serratia were about seven times easier to inactivate. Having established the relative susceptibility, they subsequently used these more rapidly growing ordinary bacteria to test the effects of high humidity on susceptibility. As previously shown by Wells, humidity over 70% greatly reduced the UV susceptibility of E. coli and Serratia. High humidity experiments were never performed with human TB or BCG. Riley hypothesized that the mycobacterial hydrophobic waxy coat might minimize the humidity effect, but decades past without this question being put to the test. We recently constructed a bench scale exposure chamber specifically to confirm Riley's studies, and to perform the humidity studies with mycobacterial species. The results show reasonable correlation with Riley's susceptibility data, highly dependent on particle size, which appears to be the variable most affected by humidity. At very high humidity (> 80%), the studies show that bacterial aerosols dehydrate incompletely, and the resulting larger particles are relatively more resistant to inactivation by UVGI. Although higher UV doses can be effective, the implications for UVGI application under high-humidity conditions remain unclear.

2. **Room-scale exposure chamber research.** Establishing UV susceptibility in a small exposure chamber, where uniform exposure of organisms to a UV dose (time x intensity) is assured, is not predictive of the effect in a room where air and organisms move unpredictably, and variable UV exposure occurs only in the upper portion of the room. Although Riley, Middlebrook and Permutt performed elegant room experiments with surrogate organisms, many questions were left unanswered[11-14]. What are the best fixture designs for various room configurations, and how should they be placed in rooms for optimal effectiveness. How can upper room UV fixtures and room ventilation interact optimally, when mechanical ventilation is present? Finally, the availability of computational fluid dynamics (CFD) has the potential to predict the interaction of room air movement and upper room UVGI, and if confirmed experimentally, allow optimal design of UVGI systems in a variety of room configurations. These experiments are underway in a full-scale experimental room at Harvard School of Public Health. As expected, greater room air mixing has again been shown to increase air disinfection in the lower room. Surprisingly, higher room temperature has been associated with greater UVGI inactivation. This finding needs to be confirmed under the more controlled conditions in the lower room. Since many parts of the world where UVGI could be applied are both hot and humid, it is possible that high temperature may mitigate to some extent the reduced UVGI efficacy due to humidity. CFD experiments are underway. Modeling UVGI-ventilation interactions has proven more difficult than expected; but promising results are beginning to appear. It will be critical to confirm CFD results by aerosolization studies in the same chamber modeled for CFD.

3. **Experimental ward.** As previously noted, Riley's experimental TB ward in Baltimore may have been the most important study of all time on airborne infection and its control. However, after 4 years the ward was reclaimed by the hospital for other uses, and many old and new questions remain unanswered. There were plans to study the efficacy of upper room UVGI, but this was never done. UV in ventilation ducts was used to prove that all of the guinea pig infections were from the experimental ward. Over a 2-year period, no guinea pigs breathing irradiated air became infected whereas the infection rate among guinea pigs breathing unirradiated air became infected at the same rate as had occurred during the first 2 years of the study. Despite variable temperature and humidity, and little if any maintenance, UVGI in the exhaust duct was 100% effective in protecting highly susceptible guinea pigs over a 2-year period. We have proposed to repeat Riley's experiment with a number of variations designed to answer new and old unanswered questions. A unique experimental design is planned to quickly evaluate the efficacy of upper room UV or any other environmental control measures. Some basic transmission questions will also be addressed. How infectious is MDR TB compared to drug-susceptible TB? When, on the best available treatment, do patients with MDR TB patients become non-infectious? What clinical characteristics predict infectiousness? Are some RFLP fingerprint patterns of TB organisms more transmissible than others?

Unfortunately, this experimental ward cannot be established in the US, or other low-prevalence country. Our current plan is to establish the ward outside of Pretoria, South Africa, in collaboration with the Medical Research Council of South Africa.

4. **Epidemiologic field trial.** Regardless of the results of experiments in bench-scale or room scale exposure chambers, or the results of studies on an experimental hospital ward, the question will remain: "Does upper room UVGI work in practice as a practical intervention to prevent the spread of tuberculosis?" UVGI could be highly effective under controlled conditions but fail to reduce transmission under field conditions, just as it failed to stop measles transmission in schools where children congregated on school buses or in crowded tenements[5]. To put UVGI to the test under field conditions, a large, multi-center, double-blind, placebo-controlled trial has been undertaken in 6 American cities[19]. The study is known as TUSS, the Tuberculosis Ultraviolet Shelter Study. The study tests at least 2 hypotheses simultaneously: that UVGI is an effective means of air disinfection, and that air disinfection in shelters (by any means) is effective. Positive results for the study requires that both hypotheses are true.

At least 2 shelters are participating in each city. Both employees and homeless persons who consent have 2-step baseline TB skin testing. Those who are negative after the second test are eligible to participate. All study shelters is fully outfitted with UVGI fixtures, but are allocated by an outside, unblinded committee of epidemiologists to be either in an active or placebo mode. Placebo fixtures have lamps that look identical to UVGI lamps, but put out no UV irradiation. Half way through the study the shelters in each city switch status, with placebo lamps being replaced with active ones, and vice-versa. Skin test conversion rates under placebo and control conditions are the study parameter of primary interest. The study is underway in New York City, Birmingham, New Orleans, and Houston. The Rio Grande Valley in Texas and Los Angeles will be the 5th and 6th cities.

Although it is too early to know anything about efficacy of UVGI, the study has already generated a great deal of data on fixture installations, reliability, lamp life, maintenance, UVGI safety, and skin test positivity rates among the homeless in several cities. Much more will be learned before the study is concluded at least 5 years from now.

Conclusion:

The study of airborne infection and its control has a long tradition at Harvard University, beginning with the pioneering work of William F. Wells and Richard Riley. Although TB control in many resource-rich countries has resulted in falling case rates, rates in many parts of the world are rising, compounded by both AIDS and multidrug resistance. Health care workers, patients, prison workers, and prisoners are among the many occupants of congregate settings where TB transmission is occurring. While effective treatment is the mainstay of TB control, environmental control through isolation of known cases and air disinfection for unsuspected cases remains a plausible, although

unproven control strategy. Current research at Harvard and other universities is attempting to better understand airborne infection and the relative value of engineering control strategies, such as ventilation and UVGI. The four-component research strategy underway at Harvard is reviewed, and its rationale explained. Although progress is being made, many more questions remain to be resolved before the promise of UVGI will be fully realized.

Type:	Source:	Sample:	Utility:
1. Bench-scale	BCG aerosol	Mech. A.S. Culture	UV dose humidity
2. Room-scale	BCG Aerosol	Mech. A.S. Culture	Fixtures, Vent/CFD
3. Hospital ward	Human M. tb	Guinea Pig/RFLP	Hospital room UV efficacy
4. Epi	Human M. tb	Skin Test	Real world UV efficacy

Figure 1 – Research strategies for Upper Room Ultraviolet Air Disinfection

References:

1.Wells WF, Riley EC. An investigation of bacterial contamination of the air of textile mills with special reference to the influence of artificial humidification. J. Inust Hyg Toxicol 1937;19:513-61.
2.Wells W. On air-borne infection: II. Droplets and droplet nuclei. Am J Hyg 1934;20:611-18.
3.Riley R, Wells W, Mills C, Nyka W, McLean R. Air hygiene in tuberculosis: Quantitative studies of infectivity and control in a pilot ward. Am Rev Tuberc Pulmon Dis 1957;75:420-431.
4.Wells WF, Wells MF, Wilder TS. The environmental control of epidemic contagion: I. An epidemiologic study of radiant disinfection of air in day schools,. Am J. Hyg 1942;35:97-121.
5.Perkins JE, Bahlke AM, Silverman HF. Effects of ultraviolet irradiation of classrooms on the spread of measles in large rural central schools. Am J Public Health 1947;37:529-37.
6.Luckiesch M. Application of germicidal, erythemal, and infrared energy. New York: D Van Nostrand; 1946.
7.Wells W. Airborne Contagion and Air Hygiene. Cambridge: Harvard University Press; 1955. 423 p.
8.Riley R, Mills C, Nyka W. Aerial dissemination of pulmonary tuberculosis - a two year study of contagion in a tuberculosis ward. Am J Hyg 1959;70:185-196.
9.Riley R, O'Grady F. Airborne Infection. New York: The Macmillan Company; 1961. 180 p.
10.Riley R, Mills C, O'Grady F. Infectiousness of air from a tuberculosis ward - ultraviolet irradiation of infected air: Comparative infectiousness of different patients. Am Rev Resp Dis 1962;84:511-525.
11.Riley R, Permutt S, Kaufman J. Convection, air mixing, and ultraviolet air disinfeciton in rooms. Arch Environ Health 1971;22:200-207.
12.Riley R, Permutt S. Room air disinfection by ultraviolet irradiation of upper air - air mixing and germicidal effectiveness. Arch Environ Health 1971;22:208-19.
13.Riley R, Permutt S, Kaufman J. Room air disinfection by ultraviolet irradiation of upper room air. Arch Environ Health 1971;23:35-40.
14.Riley R, Knight M, Middlebrook G. Ultraviolet susceptibility of BCG and virulent tubercle bacilli. Am Rev Resp Dis 1976;113:413-418.
15.First M, Nardell E, Chaission W, Riley R. Guidelines for the application of upper-room ultraviolet germicidal irradiation for preventing transmission of airborne contagion - Part II: Design and operations guidance. ASRAE Transactions 1999;105:(in press).
16.First M, Nardell E, Chaission W, Riley R. Guidelines for the application of upper-room ultraviolet germicidal irradiation for preventing transmission of airborne contagion - Part I: Basic Principles. ASHRAE Transactions 1999;105:(in press).
17.CDC CDC. Guideline for preventing the transmission of Mycobacterium tuberculosis in health-care facilities, 1994. Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 1994;43(RR-13):1-132.

18.Edlin BR, Tokars JI, Grieco MH, Crawford JT, Williams J, Sordillo EM, Ong KR, Kilburn JO, Dooley SW, Castro KG and others. An outbreak of multidrug-resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome [see comments]. N Engl J Med 1992;326(23):1514-21.
19.Brickner P, Vincent R, Nardell E, Pilek C, Chaisson W, First M, Freeman J, Wright J, Rudnick S, Dumyahn T. Ultraviolet upper room air disinfection for tuberculosis control: an epidemiological trial. J Healthcare Safety, Compliance, and Infec Contr 2000;4(4):123-131.