FINAL PROGRESS REPORT

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LIST OF TERMS AND ABBREVIATIONS

ACGIH	American Conference of Governmental Industrial Hygienists
AIR	Airborne Infections Research Facility, Pretoria, South Africa
ASHRAE	American Society of Heating, Refrigerating and Air Conditioning Engineers
BCG	Bacillus Calmette–Guérin
BWH	Brigham and Women's Hospital
CAD	Computer assisted design
CADR	Clean air delivery rate
CFD	Computational fluid dynamics
CSIR	Council for Scientific and Industrial Research, Pretoria, South Africa
DC	Direct current
DGHE	Division of Global Health Equity
DOD	US Department of Defense
EGUV	Eggcrate ceiling GUV
EWNS	Engineered water nanostructures
FAST	Find [TB] cases Actively, Separate temporarily, and Treat effectively
GUV	Upper room germicidal ultraviolet air disinfection
HEPA	High efficiency particulate air
HSPH	Harvard School of Public Health
LED UV	Light emitting diode ultraviolet
MDR TB	Multi-drug resistant tuberculosis
Mtb	Mycobacterium tuberculosis
NIH	US National Institute of Health
NIOH	National Institute of Occupational Health, South Africa
NIOSH	US National Institute of Occupational Safety and Health
NSS	Normal saline solution
PCR	Polymerase chain reaction
PG	Propylene glycol vapor
PI	Principal Investigator
TB	Tuberculosis
TEG	Triethylene glycol vapor
USAID	United States Agency for International Development
UV	Ultraviolet
UVGI	Ultraviolet germicidal irradiation
WHO	World Health Organization
XDR TB	Extensively drug resistant tuberculosis

Abstract

Project Title: ***Testing Novel Interventions to Protect Workers from Airborne Infections***

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Background: A decade ago, our original proposal was stimulated by NIOSH concerns about the spread of SARS in the workplace, pandemic influenza, bioterrorism agents, and other airborne infections. Globally, however, tuberculosis (TB), an exclusively airborne infection, remains *the greatest infectious killer of adults*. Traveling to high-risk settings abroad, US military, medical, humanitarian, and research workers as well as students are increasingly exposed to drug resistant TB. US health care workers continue to be at increased risk of TB compared to the general population. Interventions that are effective in preventing TB are likely to be even more effective against less well environmentally adapted agents such as influenza. Although we tested one novel approach, our greatest impact has been the testing and optimization of established control strategies: prompt and effective treatment of source cases, surgical masks, and upper room germicidal ultraviolet (GUV) air disinfection in congregate settings. GUV has become an increasingly important intervention as climate change results in greater use of ductless cooling systems requiring the closing of windows with reduced natural ventilation. Although GUV technology is over 70 years old, it has been poorly implemented for reasons that this research project has successfully addressed.

Specific Aims *(renewal)*: 1) to test the impact of new, more energy efficient upper room GUV systems; 2) to test propylene glycol (PG) vapor for airborne infection control; and 3) to test nebulized cationic solution (normal saline solution) as a method of reducing infectiousness of patients with MDR TB.

Description/Methods: Both bench scale and room scale test chambers at the Harvard School of Public Health (HSPH), and the unique human-to-guinea pig Airborne Infections Research (AIR) facility in South Africa were used to test the efficacy of the novel (and conventional) interventions listed below to prevent airborne transmission of TB. Building on prior NIOSH-funded research, we tested propylene glycol (PG) vapor, a lower dose of upper room GUV, eggcrate and LED GUV. Additionally, our efforts to characterize LED UV output using the bench-scale HSPH test chamber continue as does our testing of real-time florescent viable particle counting to measure the impact of GUV on air disinfection.

Results: 1) Although PG was effective in our room scale test chamber, the logistics of maintaining the PG fog at sufficiently high concentrations rendered it an impractical intervention; 2) a lower GUV dose study showed equally high efficacy in the AIR facility, suggesting a potentially more sustainable but equally effective lower dose strategy; 3) based on high efficacy in room-scale studies, an eggcrate GUV pilot test is planned in a hospital ward in Pretoria, South Africa, but hampered by delays in calibrating our viable particle counter in Boston; 4) a new South African treatment regimen did not stop XDR-TB transmission over the first 11 days in related (NIH-funded) research, emphasizing the need for environmental controls. We have not tested inhaled normal saline in patients to reduce transmission. Although promising when proposed, commercial development of more effective airway lining fluid modifying agents has ceased, and this approach has become a lower priority.

Significant or Key Findings

1. **Progress in evidence-based upper room germicidal ultraviolet (GUV) air disinfection.**
   a) An important specific aim of our NIOSH-funded airborne infection intervention studies was to provide a long-sought evidence basis for upper room GUV efficacy. Our initial published study showed that ***upper room 254 nm GUV was more than 80% effective*** in a real hospital setting, using human-to-guinea pig quantitative air sampling at the South African AIR Facility. Guinea pigs are necessary because mechanical air sampling for naturally generated *Mtb* is not possible. A second study in the renewal project demonstrated comparable efficacy at 1/3 lower GUV dose.
   b) ***"Eggcrate ceiling" GUV*** **(EGUV)** was developed and tested as a novel, more efficient approach to upper room GUV. The concept with test results was published under NIOSH and Fogarty International funding.
   c) ***LED UV:*** The promising future of sustainable upper room GUV air disinfection will most likely be based on LED GUV rather than the conventional mercury GUV lamps - the only practical and relatively inexpensive germicidal source for the last 70 years. As LED UV prices drop and power increases, the lack of mercury waste, design flexibility, ability to focus a beam without inefficient louvers, and ability to run on low DC current with solar power and battery backup all promise a potential revolution in GUV air disinfection applications in low and high burden settings alike. We have pioneered the testing for LED GUV from the beginning and are now working with the industry leader (Crystal IS) to test the world's first prototype LED GUV fixtures. Due to the unfortunate loss of our Boston-based room-scale test chamber, these studies could not be done under this grant as had been planned. Preliminary bench-scale LED GUV studies have been carried out, but not yet published.
   d) **Four other GUV developments** accomplished and published under NIOSH funding are: 1) the development and testing of a *meter sleeve for GUV lower room testing for worker eye safety*, as specified in the ACGIH standard, but not previously implemented or documented; 2) the development of a *direct method of measuring total fixture GUV output – essential for our new room dosing strategy*; 3) the *modification and validation of a CAD lighting program (Visual)* for dosing GUV in rooms; and 4) the development and testing of an entirely new, more efficient GUV fixture design – the *Brandston* fixture – named after its designer.
2. **Surgical masks on patients**
   Surgical masks were introduced to reduce transmission during the 1918-19 influenza pandemic, but their efficacy has never been quantified until our study. Using the unique AIR Facility controlled intervention model, we demonstrated that simple surgical masks were 53% effective in reducing the infectiousness of *M.tuberculosis* in ward air. This was a specific aim of our original NIOSH proposal.
3. **Room air cleaners:** A specific aim of our first NIOSH proposal was to quantify the effectiveness of room air cleaners against airborne infection. After market research, we purchased high quality HEPA air cleaners. In two separate studies, despite clean air delivery rates that should have been effective, using the same controlled AIR Facility studies, these air cleaners reduced transmission no more than 20%. The repeat study was to eliminate any possible errors in the previous study, but the results were no better.
4. ***Nebulized cationic solution*** **(normal saline)** inhaled by MDR-TB patients was proposed to reduce *Mtb* transmission to guinea pigs in the AIR facility, acting non-specifically to reduce exhaled particle generation. This was a specific aim of the renewal grant, stimulated by the commercial development by *Pulmatrix* of "iCALM," a dry-powder inhaled calcium carbonate with potent respiratory lining fluid modifying properties. However, development has since been discontinued. Without a commercial dry powder product, should sodium chloride show efficacy, this approach became a lower priority compared to more promising GUV research.
5. ***Propylene glycol (PG) vapor,*** a specific aim of the renewal grant, was tested in the Harvard roof-top bioaerosol chamber for airborne infection control in collaboration with the company developing the product. As reported in earlier progress reports, we replaced triethylene glycol vapor (TEG) with propylene glycol (PG), understood to be easier to control than TEG. Although the results were promising, the logistics of maintaining high levels of PG even in a test chamber were extremely challenging and seemed highly dependent on temperature and humidity, often not controllable in high-burden low-resource parts of the world.
6. ***Unanticipated key findings:*** Not in our Specific Aims, our NIOSH-funded studies led to important basic observations on the transmission of *M. tuberculosis* and how it can best be controlled: 1) Naturally infected guinea pigs (AIR Facility) unlike laboratory-infected guinea pigs, demonstrated transient infection – that is, many animals showed evidence of

clearing the infection; 2) Effective treatment of multidrug resistant *M. tuberculosis* patients almost immediately stopped transmission from humans to guinea pigs. The significance of these findings is detailed below.

Translation of Research Findings

1. **New GUV Guidelines:** Our controlled upper-room GUV research has led to novel dosing guidelines based on ***total fixture output per cubic meter of room volume (initial study 17 mW/m^3, subsequently reduced to 12 mW/m^3*)**. The 2009 published NIOSH guideline was based on fixture *input* wattage (which does not account for fixture efficiency) or *upper room average UV flux* (which is difficult to measure or predict). The **new South African Guidelines** (influencing all of Africa) are based on our published study, as will be forthcoming revised ASHRAE and WHO guidelines for use worldwide (**intermediate outcome**). We repeated the GUV study at approximately **12 mW/m^3** total fixture output (2/3 the 17 mW/m^3 room volume of our published study) and ***found equal efficacy*** compared to our original published study. Moreover, we used entirely locally produced (South African) fixtures for the first time. *Reducing the dosing requirement by 1/3 and using local fixtures is an important step toward more sustainable GUV application*.
2. "**Eggcrate ceiling GUV (EGUV)"** By eliminating tightly spaced louvers, EGUV greatly increases the efficiency of upper room GUV. It is an important advance for applications with high (4 m) ceilings, allowing for *one unlouvered* conventional GUV fixture to do the work of *7 highly inefficient louvered* fixtures. This cost-saving will be a key sustainability advantage for global GUV implementation (**potential outcomes**)**.** The low ceiling at the current AIR facility did not allow for the installation and testing of EGUV. However, we requested and received permission to purchase a viable particle counter (Biovigilant) which has been used to test upper room GUV in classrooms in Indiana. Thus far the device is being tested by our Fogarty research fellow in Boston, but it will ultimately be shipped to South Africa where it will be used to test the first Eggcrate GUV installation in a real hospital (Tshwane District Hospital) under a contract with our partner, Council for Scientific and Industrial Research (CSIR). Future studies are planned in a newly opened microbiological test chamber at the South African National Institute of Occupational Health, the South African equivalent of NIOSH.
3. ***Unanticipated key findings and their translation:*** In the course of our first 5 NIOSH-funded AIR facility studies, infection rates under control conditions (no interventions) varied greatly, from 1 of 90 guinea pigs infected (<1%) to 77% of 90 guinea pigs infected over exposures ranging from 2 to 4 months. The mystery was solved when molecular fingerprinting studies from guinea pig *Mtb* isolates showed that transmitted strains were all *unsuspected* Extensively Drug Resistant (XDR) *Mtb* not on effective therapy, and that the one study with one guinea pig infection from 26 patients over 3 months had no unsuspected XDR TB-patients. Effective MDR treatment rapidly suppressed transmission from MDR patients – not XDR.

Most TB transmission control efforts focus on *known* TB patients, most of whom are on effective therapy, whereas there is evidence that most transmission occurs from *unsuspected* cases of TB, or known TB with *unexpected and unproven drug resistance*. Therefore, the most effective TB transmission control strategy in institutions would likely be **to *re-focus efforts from known cases to finding unsuspected cases,*** diagnosing them rapidly with molecular diagnostic testing, including rapid drug susceptibility testing – with rapid initiation of effective therapy. *We have named this strategy **F-A-S-T**, for **F**ind Cases **A**ctively, **S**eparate temporarily, and **T**reat effectively based on rapid molecular testing*.

Research Outcomes/Impact

1) **GUV -** Under 10 years of NIOSH funding, we have advanced the evidence-based implementation of GUV air disinfection more than all previous GUV research put together. Highly effective GUV can now be planned based on a rational total fixture output/room volume basis, and fixture output can be measured directly. Alternatively, GUV can be modelled in Visual-UV, and safety monitored with a meter sleeve. LED and Eggcrate ceiling GUV can increase efficiency, and a new more efficient suspended fixture design has been published.
2) **Surgical Masks** – first quantitative evidence on efficacy applicable to airborne influenza as well as *M. tuberculosis*.
3) **Room Air Cleaner and Propylene glycol vapor** – *not* found to be effective.
4) **Important incidental observations:** a) *Effective treatment* – USAID has embraced the **FAST strategy** and has funded many pilot FAST projects around the world (**intermediate impact**). b) *Transient TB infection* – vaccine and host-directed therapy development – leading to a DOD proposal for reducing risk of *M. tuberculosis* for military and other personnel traveling to high risk countries.

Scientific Report

The scientific research results of our NIOSH-funded project have mostly been published, as evident in the bibliography, and it would be duplicative to report that work again here in detail. Instead, this narrative puts our research findings and their significance into context in more detail than in the above summary, citing our principal papers (citations refer to the publication list). The *unpublished* exceptions are: 1) two failed attempts to test GUV under sustained high humidity in our experimental hospital ward; 2) two controlled AIR Facility studies of room air filtration machines which did not demonstrate significant efficacy for reasons that remain elusive. We still plan to publish these because of current evidence-free reliance on room air cleaners in many hospital settings around the world; 3) our propylene glycol vapor study which produced significant room air disinfection but was not logistically practical to implement. However, in collaboration with the company we did produce a project report which was shared with NIOSH previously; 4) our second upper room GUV efficacy study showing comparably high efficacy at a 1/3 lower GUV dose (total fixture output per m^3 room volume) – we intend to publish – but essentially identical to our published study in methods and analysis. We include some papers and discussion not directly under NIOSH funding to emphasize the translational importance of the last 10 years of NIOSH funded studies – well beyond what was in the specific aims. These include incidental observations on the impact of effective treatment that have resulted in a new, widely implemented approach to institutional TB transmission control strategy called FAST. These incidental observations of transient infections in guinea pigs stimulated a Gates-funded vaccine trial and a new DOD host-directed therapy proposal. Finally, WHO is in the process of revising its TB Transmission Control evidence-based policy, with a meeting in Geneva in March 2018. Our published controlled studies of surgical face masks and GUV, and the impact of treatment on transmission resulting in FAST are among the most evidence-rich interventions that will be reviewed.

GUV efficacy, dosing guidelines, and innovations. Upper room germicidal UV (GUV) is a powerful, sustainable, safe, and highly effective technology that has suffered from poor implementation around the world. Among the reasons for poor implementation have been: 1) little data on efficacy in clinical settings; 2) lack of practical evidence-based guidelines; 3) little progress in fixture design efficiency, standardization, or measurement; 4) no validated CAD program for GUV: 4) concerns about GUV safety for room occupants; 5) limited technical know-how where needed; and 6) poor field maintenance infrastructure. Over the course of 10 years of NIOSH-funded studies at Harvard and at the South African Airborne Infections Research (AIR) Facility we have addressed many of these deficiencies, although full global implementation will require considerable market research, advocacy, technical training, and collaborations with industry.

A main specific aim in our original proposal was to conduct a fully controlled field trial of upper room GUV in a hospital setting - the AIR Facility, where large numbers of guinea pigs serve to quantify *M. tuberculosis* concentrations in air – not quantifiable by conventional culture or pcr-based air sampling. Escombe conducted a similar study in Lima, Peru, based on our model and with our technical assistance in the planning phase. Our goal was not only to independently confirm the high efficacy found in NIOSH-funded chamber studies (Miller, et al), and the field study reported by Escombe, but also to carefully translate the dose used in the study to evidence-based guidelines that would be practical to implement. NIOSH had funded chamber studies by Prof. Shelly Miller et al. and, based on the results, published guidelines in 2009. Those guidelines used fixture *input wattage* for dosing, which did not account for *variable fixture efficiency*. It also used average upper room GUV flux, an output measure, but there is no standard method to measure average upper room GUV flux, and, moreover, predicting average upper room GUV flux before an installation was not possible. Our research to develop and test a CAD program for UV, based on the visible light program, *Visual*, was an effort to be able to predict average upper room GUV flux, and many other important parameters. However, it requires

full gonioradiometry of fixtures as input – and that did not exist for any fixture – leading to collaboration with Acuity Lighting and several published papers here.

The first GUV study proved highly successful. The AIR Facility worked perfectly for the purposes for which it was designed – testing interventions that could be applied every other day – so that rates of guinea pig infections could be determined by long-term breathing of the air by guinea pigs in two identical chambers sampling ward air every other day. In this case, GUV was turned on in the patient rooms and corridor every other day and exhaust air was delivered, alternating every other day, to the two guinea pig exposure chambers, "control" and "intervention". At the end of several months exposure, the risk ratio for infection, based on tuberculin skin testing, in the chamber receiving control exhaust air was 4.9 compared to the chamber receiving exhaust air on the days when upper room GUV was on. This was equivalent to 80% protection from infection. When a correction factor for greater multiple hits in the control room was applied – the protection rose to about 83%. This was the equivalent protection calculated by adding 24 room air changes over and above the 6 baseline air changes per hour in the patient rooms.

In addition to demonstrating efficacy, we were intent on finding a rational approach to applying upper room GUV so that others could expect similar results. We came up with two such approaches. The simplest approach, based on a paper by Rudnick and First, was to simply calculate the total GUV output of the fixtures used and the total volume of air disinfected. First, we needed to know the total fixture output of the two fixtures used, one of each in each room. We used two different fixtures so that neither manufacturer could use our study to advertise their fixtures to the disadvantage of other manufactures. But, using two fixtures and measuring their output allowed us to focus on their differences in design and function. The total GUV output was 17 mW per m^3 room volume. (6)

Fixture Design: In our published GUV study, one fixture had a number of design advantages over the other – resulting in 10 times greater efficiency. Since all but the most parallel GUV rays coming off the front of a conventional mercury vapor lamp are trapped in the louvers designed to prevent occupant exposure in the lower room, a well-designed parabolic reflector is required to capture and redirect GUV rays from the rear of the lamp. Given the limited availability of gonioradiometry and its uncommon application to measuring total GUV output, Dr. Rudnick in our group published a direct measurement technique for louvered fixtures and validated the results compared to the same fixtures measured by gonioradiometry or integrated sphere, another laboratory approach to total fixture output.(2)

GUV dosing: A second, not yet published GUV study using the same experimental protocol tested a 1/3 lower GUV dose and got similar good efficacy, resulting in a lower dose recommendation of 12 mW per m^3 room volume for upper room GUV guidelines issued by South Africa, and forthcoming guidelines by ASHRAE and WHO for global application. In addition, for sustainability, we made it a point to use South African produced GUV fixtures which had been redesigned and tested to meet output requirements. In a future funding request, we will propose defining additional dosage points on an as yet incomplete dose-response curve for applying upper room GUV. Our first paper was accompanied by an editorial by Prof. Shelly Miller, the PI of the NIOSH-funded chamber studies, acknowledging that with this work we had now set the stage for widespread implementation.

Innovation: As noted, traditional louvered GUV fixtures (wall or suspended) used for ceiling heights under 3 m are grossly inefficient, converting as little as 0.6% to 6% of electricity into useful GUV output for air disinfection. Most of the GUV rays are immediately captured by the louvers. We designed and tested a new approach to upper room GUV where a lamp with a parabolic reflector but without louvers could produce GUV rays above a protective "eggcrate" ceiling like those used in airports, allowing upper and lower room air to mix, but preventing angled rays from entering the occupied space. Studies suggested that removing louvers would increase efficiency at least 7-fold. Essentially, GUV rays are

employed for air disinfection before being blocked from entering the lower room, not after. Eggcrate GUV was installed and tested against aerosolized organisms and the results published. Even in a prototype state, eggcrate ceiling GUV proved many times more efficient than conventional louvered GUV fixtures. A limitation is the custom design required for the eggcrate ceiling approach, which adds considerable cost to GUV air disinfection. Future work will attempt to produce fixture-like fabricated floating "eggcrate" panels in an effort to realize the efficiency of eggcrate ceilings without custom fabrication of an entire eggcrate ceiling. (9)

New fixture design. Awareness of the critical importance of fixture design to total GUV output resulted in Howard Brandston, a high-level fixture designer (and volunteer consultant), contributing a new fixture designed to capture rays from both the front and rear of a fixture, thereby increasing output. The "Brandston" fixture has been tested, and published, but is not yet produced by any manufacturer even though it is not protected by patents. (1)

LED GUV. The future of GUV is almost certainly LED due to its distinct advantages of long life, battery and solar power, absence of mercury waste, and wavelength closer to peak germicidal activity. Although we proposed LED testing, product development and the loss of our test chamber at HSPH have delayed testing, which is now planned for South Africa. We are currently testing the bactericidal advantage of 265-270 nm wavelength GUV compared to mercury vapor 254 nm.

Other technical accomplishments – measurement and modeling:

1) Aerosol chamber studies – source location. Performing extensive chamber bioaerosol studies to test GUV fixtures resulted in the observation that the bioaerosol location and fan direction distorted experimental test results, unrelated to overall efficacy in the chamber. (10)
2) Occupant safety GUV measurements. Even though ACGIH guidelines suggested a "sleeve" around the GUV detector to mimic the eye protection from overhead GUV of the skull and brow anatomy, it had never been done as far as we knew. Without the sleeve, meter measurements suggested higher exposure than actually experienced by the eye – the most UV sensitive structure. We produced, tested, and published the results of safety measurements with and without both a makeshift and professionally made sleeve. A fixture manufacturer now sells a sleeve based on this work and the ACGIH recommendation. (3)
3) Visual and gonioradiometry. Adapting gonioradiometry for visible light to GUV was not trivial and was accomplished in collaboration with scientists at Acuity Lighting. The method has been published. (14,15)
4) Direct GUV fixture output. Already mentioned, the Rudnick direct measure of total fixture output for louvered fixtures was published as an alternative for quick measurements when integrating sphere and gonioradiometry are unavailable. (2)
5) Fan modeling. One of our first Fogarty fellows, S. Zhu, working through NIOSH funding, developed a mathematical modeling approach to the ceiling fans recommended to achieve good air mixing. He produced several papers on the subject that have been used by other modelers of upper room GUV. (11,13)
6) Biovigilant on-site testing for GUV efficacy. Based on a publication by Lau using a viable particle counter to determine upper room GUV efficacy in a school, we purchased a biovigilant machine for testing in Boston and South Africa. Currently we are trying to correlate the time frame for GUV viability readouts by viable particle counting vs. culture before doing room studies.

Other tested interventions: surgical masks on patients and room air cleaners:

Surgical masks on patients. One of our original specific aims was to study the impact of surgical masks on patients on TB transmission. The use of surgical masks as source-control was introduced during the 1918-1919 flu pandemic, but efficacy was never proven. Without the AIR facility controlled experimental design, such a clinical trial would be

impossible. However, we were able to ask patients to wear surgical masks every other day and send exhaust air every other day to control and intervention guinea pig exposure chambers. The results showed that exhaust air was 53% less infectious on days when surgical masks were used most of the time – the exception being while eating. Air was not sampled at night since patients generally do not sleep with surgical masks. Surgical masks are intended for short term use on TB suspects before effective therapy is started. It also mimics cough hygiene since in both cases, the active intervention is a physical barrier blocking the exit of large respiratory particles before they evaporate into droplet nuclei. Cough hygiene has never been rigorously tested re: its efficacy, but we speculate that it is not likely to be more effective than surgical masks enforced under clinical trial conditions. (16)

Room air cleaners, with HEPA filtration, GUV, or both, are widely marketed around the world as a quick and easy approach to air disinfection. Sales pitches focus on the ability of single pass removal of infectious particles. While a few studies document some efficacy with bioaerosol testing, more often than not, in the field, the effective clean air delivery rate (CADR) is often low relative to room volume, resulting in the addition of very few equivalent air changes per hour. We tested several high volume, nearly silent HEPA filter room air cleaners sized to produce approximately the equivalent of 16 ACH ventilation. We were surprised when test results in the AIR facility indicated a mere 20% reduction in infectiousness of exhaust air on days when room air cleaners were in use. We repeated the study with similar disappointing results. Careful checks for air leakage around filters, and analysis by CFD failed to explain the poor test results. Short circuiting of air is one possible explanation. We have not yet published these negative results, but intend to.

Important observations made during NIOSH-funded studies, but not part of the specific aims.
In a series of NIOSH-funded intervention studies in the AIR facility, transmission under control (non-intervention) from smear positive TB patients was highly variable from one study to the next. This ultimately was shown to be largely due to the rapid and profound impact of treatment – if effective. In one 3-month exposure study, only one guinea pig infection occurred following exposure to 26 presumed infectious patients with presumed MDR TB and just recently started on standard South African MDR treatment. That treatment was effective, and unlike 4 other control cohorts where transmission occurred at much higher rates, there were no unsuspected XDR (extensively drug resistant) TB patients in this control cohort. As Riley had shown 70 years before, effective treatment rapidly stops TB transmission. This observation was then translated to the FAST initiative – a refocused, intensified administrative approach to TB transmission control. (12)

Misdirected TB transmission control: CDC recommended that approaches to TB transmission control focus primarily on newly diagnosed patients, specifying isolation criteria, ventilation flow rates, airflow direction, and respirator usage. However, most such patients are started on therapy, and both old and new studies suggest an almost immediate cessation of transmission IF treatment is effective. If patients on therapy are not the source of transmission in hospitals, what is? There is adequate demonstration around the world that under high prevalence conditions, patients with unsuspected, untreated TB, and patients with known TB, but unsuspected drug resistance are likely to be the major source of transmission.

FAST: With the advent of rapid molecular diagnosis of TB and TB drug resistance, the potential exists to screen every patient admitted to a hospital with cough (or other screening criteria) for TB and if positive, immediately determine if treatment is effective. Therefore, our NIOSH-funded studies on airborne transmission intervention indirectly led to a refocus on transmission from unsuspected TB cases and FAST, a refocused, intensified approach to institutional TB transmission control. FAST stands for, **F**ind cases **A**ctively by cough screening, **S**eparate temporarily, and **T**reat effectively based on molecular DST. FAST is being widely implemented with the help of USAID funding around the

world, from Vietnam to Africa, Peru, Bangladesh, and parts of Russia to name a few pilot projects. Vietnam is planning country-wide implementation. In an NIH-funded study in Peru we are testing the hypothesis that FAST implementation will reduce TB transmission to medical and nursing interns and emergency department staff. (7)

Another important NIOSH-funded observation not in our specific aims, but coming out of AIR facility intervention studies is transient TB infection in the guinea pig. Prior to this publication (17), laboratory aerosol infected guinea pigs (30-50 cfu dose) all progressed to disease and died. Naturally infected (human-to-guinea pig) guinea pigs did not die and many did not remain infected. The ability of the highly susceptible guinea pig to resist persistent infection motivated the Gates Foundation to fund an AIR study of BCG to prevent infection. It has also motivated a new Department of Defense (DOD) proposal to test host-directed-therapy in the AIR facility. Evidence that metformin or a statin could prevent persistent TB infection through macrophage stimulation would have great implications for the field.

Novel approaches to airborne infection control

Glycol vapors. We proposed testing Triethylene glycol (TEG) vapor in the HSPH test facility following commercial interest in overcoming delivery barriers. Earlier literature is rich in papers showing efficacy, but the approach was never adapted, and never tested for TB. Together with the company, but using propylene glycol vapor (PG, easier to handle), we conducted studies showing some efficacy, but serious logistical problems in maintaining effective vapor levels. We did not think PG or TEG had potential as practical interventions for institutional TB transmission control.

Inhaled normal saline. With the Edwards group, we published a paper showing that inhaled normal saline reduces the generation of respiratory particles. A company was developing an even more effective calcium carbonate inhaled salt that they planned to market as iCALM for transmission control. However, during the course of this funding cycle, the company decided not to develop iCALM because of poor motivation for patients to take something to prevent transmission. Since normal saline solution (NSS) was less effective than iCALM, we decided there was no point in testing normal saline as proof of principal, but to focus on improving GUV where there was a clear pathway forward.

Engineered Water Nanao-structures (EWNS). A publication on EWNS led by Demokritou was not NIOSH-funded, but is mentioned because plans are to test this novel approach in a future NIOSH funding proposal. (8)

Personal occupant CO2 measurements to assess buildings

Not part of our NIOSH specific aims, we have been testing the concept of personal CO2 monitoring to assess the potential for airborne transmission in buildings. Personal CO2 monitoring integrates both ventilation and occupancy. Early studies under Fogarty funding look promising. We mention it here because we plan to request funding to integrate CO2-controlled GUV air disinfection.

Included below are examples of review articles largely based on NIOSH-funded research findings. (4,5)

CITATIONS

(including publications related to direct NIOSH-funded projects)

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