Non-Vaccine Acute Respiratory Disease Prevention Interventions (NOVARDPI): A Literature Review

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Agenda

- Introduction: Respiratory Diseases
  - Important Characteristics
- NOVARDPI Definition
- Search Methodology
- Rating the NOVARDPIs
- Discussion/Results
- Conclusion

Introduction: Respiratory Diseases

- Respiratory diseases are among the most prevalent of diseases.
- Acute Respiratory Diseases (ARDs) are highly communicable.
  - Can result in explosive outbreaks due to high infectivity
  - Rapid transmission from a common source or by person-to-person spread in susceptible populations.
    - Aerosol spread
    - Person-to-person contact (e.g., shaking hands)
    - Fomites (doorknobs)

Introduction: Respiratory Diseases

- The Influenza pandemic of 1918-1919 quickly spread from Camp Funston, KS, to the rest of the US, Europe and then throughout the world.
  - Estimates of deaths are in excess of 20 million worldwide, easily exceeding all the deaths in WWI.
- The resurgence of resistant tuberculosis in the United States occurred in part with the growth of a susceptible population, those with Acquired Immunodeficiency Syndrome (AIDS).

Introduction: Respiratory Diseases

- Another important characteristic of ARDs is the often large variability of their genetic composition.
  - Influenza has yearly genetic drifts that require worldwide surveillance for predicting the components of the yearly vaccine. Periodic genetic shifts make even the most regularly immunized population groups such as the US military susceptible.
  - There are hundreds of strains of rhinoviruses and corona viruses.
- Creation of effective vaccines can be very difficult

Introduction: Respiratory Diseases

- The range of symptoms for ARDs can be very broad, from nuisance symptoms like the common cold to deadly symptoms like influenza or meningococcal disease.
- ARDs with mild symptoms often go unnoticed by the general public.
  - Lack of interest can mean lack of a pharmaceutical "market" and, lack of interest from vaccine makers.
  - Example: mild adenovirus (ADV) infections in military recruits was unprofitable for Wyeth Ayerst and ADV 4 & 7 vaccines were discontinued in 1997 despite proven efficacy and cost effectiveness.

Introduction: Respiratory Diseases

- With the loss of ADV vaccines, in 1999 the US military (Army, Navy and later on the Air Force) began experiencing ADV incidence rates similar to the pre-vaccine era in the 1960's.
- Despite US military attempts at Non-Vaccine ARD Prevention Interventions (NOVARDPIs), the epidemics continue.
- We conducted a literature review of NOVARDPIs to determine which ones may be the best candidates against current or future ARDs without known vaccines.

Literature Review Methodology

- We conducted a review of the literature on NOVARDPIs (published and unpublished) beginning in 1997 and updated in April, 2000.
- We used the following search terms:
  - Ventilation and Health or Respiratory Disease
  - UV or Ultraviolet and Health or Respiratory Disease
  - Antibiotics and Health or Respiratory Diseas
  - Handwashing or Handwipes or Hand and Wash and Health or Respiratory Disease

Literature Review Methodology

- Additional search terms:
  - Disease Transmission
  - Filtration or Filter
  - Airplane and Infection
  - Military Health or Troops or Army or Navy or Air Force or Marines
  - Adenovirus
  - Bicilin/Benzathine Penicilin G
  - Macrolides (Azithromycin, Clarthromycin)
  - Interferon

Literature Review Methodology

- Additional search terms:
  - Amantadine, Ramantadine
  - Neuramanidase Inhibitors (Zanamivir and Oseltamivir)
  - Zinc
  - Vitamin C
  - Echinacea

Literature Review Methodology

- Additional search word criteria:
  - Infection
  - Respiratory
  - Cold(s)
  - Flu(s)
  - Pneumonia
  - Fever or Febrile
- In all, we reviewed over 140 published and unpublished studies or descriptions of NOVARDPIs.

Rating the NOVARDPIs

- To categorize the merit of each of the NOVARDPIs covered by the many different articles, we assigned the following 2 alpha-numeric ratings.
- The first code was a letter ranging from A to D and reflects the scientific merit or validity of the NOVARDPI as supported by papers or studies.

Rating the NOVARDPIs: 1st Code

Codes	NOVARDPI's Supporting Study(ies) Design and Methodology
A	Well-designed experimental or epidemiological study(ies) with controls and properly executed without significant possible bias.
B	Experimental or epidemiological study(ies) with controls and fairly executed without significant possible bias.
C	Experimental or epidemiological study(ies) with some control comparison, that is fairly executed.
D	Studies with no control comparisons, poorly executed, or involving the possibility of significant possible bias.

Rating the NOVARDPIs

- The second code was a number ranging from 1-4 and reflects the efficacy, cost-effectiveness, or feasibility of implementation of the NOVARDPI.
- NOVARDPIs that were rated as a “C” or lower brought into question the final conclusions of the studies’ efficacy, cost-effectiveness, or feasibility of implementation.
  - As a result, any NOVARDPI that had a “C” rating could not have a second code rating higher than 2.

Rating the NOVARDPIs

- NOVARDPIs with studies that did not measure efficacy, cost-effectiveness, or feasibility of implementation were coded as a “9.”
- All NOVARDPIs rated as a “D” were given a second code of “9.”

Rating the NOVARPIs: 2nd Code

Codes	NOVARDPIs Efficacy, Cost-Effectiveness, Feasibility of Implementation
1	Strong efficacy, cost-effectiveness, or feasibility to implement
2	Slight efficacy, cost-effectiveness, or feasibility to implement
3	Marginal efficacy, cost-effectiveness, or feasibility to implement
4	Poor efficacy, cost-effectiveness, or very difficult to implement
9	Unknown efficacy, cost-effectiveness, or feasibility to implement

Results and Discussion: Infection Control Section

- C3 - Handwashing
  - In 1861 Semmelweiss noted the spread of nosocomial infections by hand.
  - The Centers for Disease Control reflecting a number of excellent studies have shown the effectiveness of handwashing against nosocomial and enteric infections.
  - However, except for specific hospital or child care settings (against respiratory syncytial virus), the CDC does not have any specific recommendations for handwashing in the prevention of respiratory diseases.

Results and Discussion: Infection Control Section

- C3 - Handwashing (cont.)
  - Of the 6 population based studies for handwashing to prevent respiratory diseases, two studies observed a decrease in rates from previous years (no concurrent control groups).
  - Only one quasi-experimental study observed a weak effect.
  - Based on these 6 studies, there is very weak evidence that handwashing can prevent respiratory diseases.
  - Potential problems: individual compliance when not near sinks and lack of cohorting.

Results and Discussion: Infection Control Section

- B2 - Antimicrobial Handwipes
  - There have been 2 experimental studies with controls.
  - One had marginal results and the other by Gibson in 1997 (unpublished) showed about a 33% reduction in sick call visits for URI among USAF squadrons using the wipes. Visits for sore throat were reduced by 40%.
  - Costs may not be insignificant. A current USAF estimates that it would cost $3,000 per month to supply 700 trainees with antimicrobial handwipes.

Results and Discussion: Infection Control Section

- C3 - Masks
  - Although there are a number of studies that determine the effectiveness of different masks to protect against specific chemicals or infectious diseases, there are a number of implementation problems with masks.
  - It is logistically impractical & expensive for all personnel to wear masks during endemic ARD season.
  - It is difficult to mask those with illness because of individuals that shed pathogens before showing significant symptoms.
  - Compliance to constant wearing of masks is difficult.

Results and Discussion: Administrative Control Section

- Administrative controls are feasible, low or no-cost actions that commanders or administrators may implement quickly to prevent, limit, or control outbreaks of ARDs.
- These controls do not involve major expenditures for equipment or other items, engineering changes, or the administration of drugs or vaccines.

Results and Discussion: Administrative Control Section

- Cohorting refers to the grouping of people according to some variable, with minimal if any contact between groups. The selection variable may be unit of training (e.g., company or platoon), evidence of illness, or a variable such as smoking which may impact on the risk of disease.
- U.S. military units practiced cohorting of recruits by training unit in the pre-adenovirus vaccine era.

Results and Discussion: Administrative Control Section

- C2 - Cohorting
  - Anecdotally, the Marines experienced success in basic training, experiencing sharply demarcated outbreaks in the winter, only to have mixing with outbreaks in advanced training.
  - The Army had no documented success, which some attributed to basic training commanders requiring large military formations in theaters and elsewhere.
  - May also cohort/isolate those that are sick but there are problems with early identification of those with minimal symptoms and ethico-legal issues in segregating smokers who have higher ARD rates.

Results and Discussion: Administrative Control Section

- D9 - Sleeping head-to-toe
  - This consists of sleeping troops in a line of bunks alternating head and foot positions.
  - This measure has a long history of military use and was practiced extensively in the pre-adenovirus vaccine era.
  - Theoretically, troops spend a significant amount of time sleeping and air exchanges in barracks are often not adequate and distance between breathing zones may reduce the spread of infectious agents.

Results and Discussion: Administrative Control Section

- D9 - Sleeping head-to-toe
  - This practice was often augmented by hanging bed sheets or tent shelter halves (sometimes call "sneeze sheets") from the ceiling so that each bunk was in a somewhat protected cubicle formed by walls of sheets or shelter halves.
  - Investigators in World War II concluded that these methods had not received a rigid test.

Results and Discussion: Administrative Control Section

- D9 - Sleeping head-to-toe
  - These methods are based on the assumption, which may be doubted, that transfer of respiratory infections occurs primarily in the barracks.
  - These method are difficult to enforce.
  - Head-to-toe sleeping practices have been adopted by the modern military with the loss of the adenovirus vaccines.

Results and Discussion: Administrative Control Section

- C2 - Minimum Space Requirements
  - Enforcing minimum space requirements to limit the effect of "contagion" goes back to the beginning of the United States Army.
  - Currently, AR 415-50 requires 72 sq. ft of net floor space (bed, locker but excludes lounges, bathrooms, general circulation, halls and stairwells) per recruit.
  - The basis for AR 415-50 goes back to influenza attack rates in troops in barracks observed in World War I.
  - There are no current studies.

Results and Discussion: Administrative Control Section

- C2 - Minimum Space Requirements
  - Compliance with AR 415-50 is tempered by available space, building configuration and training unit size.
  - Good, contemporary studies could have an impact on future barracks design and construction.
  - Even if complied with in the barracks, minimum space requirements are not adhered to in classrooms, auditoriums, or mess halls.

Results and Discussion: Administrative Control Section

- D9 - Dust Control
  - The concept is that the routine cleaning of floors in troop housing (barracks) areas reduces the amount of airborne dust and associated resuspension of inhalable viral particles for training personnel.
  - This is a widely practiced Public Health measure not for the control of ARDs, but in the prevention of Hantavirus infections based on the military experience gained during the Korean War and subsequent CDC recommendations following the Hantavirus Pulmonary Syndrome outbreak in the 4 Corners Region in 1992.

Results and Discussion: Engineering Section

- C4 - Ultraviolet (UV) Sterilization of Air
- C4 - Glycol Vapor Sterilization of Air
  - In April 1944, the Armed Forces Epidemiological Board (AFEB) meeting records that while there was slight efficacy of both ultraviolet or glycol vapor sterilization of the air for ARDs, the discomfort, cost, and impracticality of the NOVARPIs were not feasible for the barracks or the hospital setting.
  - Only the facilities with the highest-risk-for-severe respiratory diseases consider UV air sterilization as practical.

Results and Discussion: Engineering Section

- C2 - Ventilation Control (Air Exchange Rates vs. Circulated Air)
  - The theory is that is that barracks that are adequately ventilated with fresh (clean) air will lead to dilution of airborne contaminants (i.e. unpleasant odors) as well as a decrease in the concentration of airborne microorganisms and dust.
  - Adequate ventilation can lead to a reduction of indoor temperature and humidity, which are both associated with increased survival of respiratory viruses, to include adenoviruses.

Results and Discussion: Engineering Section

- C2 - Ventilation Control (Air Exchange Rates vs. Circulated Air)
  - No amount of ventilation, however, will compensate for overcrowding (appropriate space allocation of 72 square feet per recruit mentioned previously).
  - In the event mechanical ventilation fails, windows should be partially opened except during extreme cold weather. Unfortunately modern energy efficient building designs often have windows that do not open.
  - Use of large, indoor fans to provide air circulation will be helpful only if there is enough air exchange where fresh air is introduced into enclosed barracks areas.

Results and Discussion: Engineering Section

- C2 - Ventilation Control (Air Exchange Rates vs. Circulated Air)
  - Ironically, industry standard for ventilation is set by the American Society of Heating, Refrigerating, and Air Conditioning Engineers based on indoor air pollutants such as body odors, CO_2, and cigarette smoke.
  - Ventilation systems should be kept clean and filters checked at least every two weeks (changed if found dirty). Microbial studies have cultured bacteria from poorly maintained ventilation systems.
  - None of the above-named ventilation control measures have been tested in controlled studies ref. ARDs.

Results and Discussion: Engineering Section

- C2 - Ventilation Control (Air Exchange Rates vs. Circulated Air)
  - Except for certain isolation rooms in hospitals, almost all buildings do not have the capability to dedicate air intake or exhaust to individual rooms. Intake and exhaust for many rooms are handled by large heating-ventilation-air conditioning (HVAC) systems.
  - Comfort and energy standards requirements are even more problematical in non-living area facilities such as classrooms, theaters, and auditoriums.

Results and Discussion: Antibiotic/Antiviral Section

- A2 - Benzathine Penicillin (BPG)
- A2 - Azithromycin
  - Used since 1953 to reduce incidence of streptococcal disease and its nonsuppurative complications, acute rheumatic fever and acute glomerulonephritis.
  - BPG has not been recommended for the prevention of ARD secondary to non-rheumatogenic streptococci.
  - Other penicillin-sensitive nonstreptococcal organisms that cause epidemic ARD have not been recognized.
  - A 1997 study by Tarlow showed that oral azithromycin outperformed BPG by 84% in preventing strep. disease.

Results and Discussion: Antibiotic/Antiviral Section

- A2 - Benzathine Penicillin (BPG)
- A2 - Azithromycin
  - Despite the biologic plausibility that the use of antibiotics may be beneficial in the prevention of other non-streptococcal causes of ARDs, this has not been studied.
  - Wide use of many different antibiotics in healthy but high-risk populations may be risky in the possible development of sensitivities or cultivation of resistant organisms.

Results and Discussion: Antibiotic/Antiviral Section

- A3 - Interferon
  - Alpha 2 interferon was shown in a controlled study to be effective in the prevention of rhinovirus infection.
  - However, in other studies, interferon had no prophylactic efficacy against parainfluenza, RSV, and coronavirus infections.
  - Douglas et al. 1986; Hayden et al. 1986 – 2 family studies showing that intra-nasal interferon had no protective effect against influenza A or B, parainfluenza or coronaviruses.

Results and Discussion: Antibiotic/Antiviral Section

- A2 - Amantadine, Rimantadine
- A2 - Zanamivir and oral Oseltamivir
  - Well-controlled clinical studies have shown the prophylactic benefits of the above antivirals in the prevention of influenza for those that were not vaccinated or those that were poorly protected by vaccination.
  - The antivirals have also been shown to decrease the length of illness when given early in the disease.
  - The above are NOVARDPIs are specific only for prevention of influenza ARDs.

Results and Discussion: Antibiotic/Antiviral Section

- D9 - Zinc, Vitamins A, C; Echinacea
  - Overall, studies on the preventive and therapeutic effects of the above substances are inconsistent.
  - Most studies show a variable reduction in the duration of symptoms, but few demonstrate prophylactic effects.

Recommendations and Conclusions

- The most promising NOVARDPIs as evidenced by their supporting studies are:
  - Antimicrobial handwipes - B2
  - Cohorting - C2
  - Minimum Space Requirements - C2
  - Ventilation/air exhchange rates - C2
  - Antibiotic prophylaxis - A2 (but specific only for streptococcal prevention)

Recommendations and Conclusions

- We recommend that more definitive studies focus on the most promising NOVARDPIs for their efficacy against the wide range of ARDs.
- We further recommend better controlled studies to evaluate the biologic plausibility of the poorly evaluated NOVARDPIs.