

EXHIBIT U



Commentary

The open-air factor and infection control

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The management of infection faces numerous challenges in the 21st century. One way to understand how to cope with these challenges is to examine how infections were dealt with in the past [1,2]. For example, in the years before antibiotics became available, open-air therapy was the standard treatment for tuberculosis (TB) and other infectious diseases. Patients were nursed next to open windows in cross-ventilated wards or put outside, in their beds, to breathe fresh outdoor air. This was believed to aid their recovery and reduce the risk of cross- and re-infection. The open-air regimen was also widely used on casualties during the First World War; and during the 1918–1919 influenza pandemic [3].

At this time, outdoor air was considered capable of killing *Mycobacterium tuberculosis*. There was support for this in the work of, among others, Dr. Arthur Ransome (1834–1922) a leading investigator of the disease [4]. Ransome emphasized the importance of fresh air in the disinfection of rooms occupied by tuberculous patients; and in the disinfection of patients themselves:

... abundant fresh air, together with sunshine, acts antiseptically upon both the bodies and the clothing of patients, destroying all organic impurities which may emanate from either, and so purifying the air that enters the respiratory organs. [5]

There appears to have been little further research on the germicidal properties of outdoor air following this period.

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During the 1950s, chemotherapy superseded the open-air regimen, and belief in the therapeutic and germicidal properties of outdoor air diminished.

Hospitals were no longer designed to exploit them. Then, somewhat ironically, in the 1960s scientists involved in bio-defence research developed a technique for measuring the effect of fresh rural air on airborne pathogens [6]. They found outdoor air to be far more lethal to them than indoor air; both during the day and at night. They used the term ‘open air factor’ (OAF) to describe the germicidal constituent in outdoor air that reduces the survival and infectivity of pathogens [7]. Initial research showed that the OAF disappears rapidly when outdoor air is enclosed [8]. However, it was later established that its germicidal properties could be fully retained in enclosures if ventilation rates were high enough [9].

One finding was that the minimum rate which fully preserved the OAF’s toxicity in a cube and a cuboid container was 30–36 air changes per hour (ach) [9]. A recent study of ventilation and infection rates in different rooms occupied by tuberculosis patients has shown that older pre-1950s hospital wards, with large windows on more than one wall and tall ceilings, had lower TB infection rates than more modern designs. Significantly, the older wards allowed ventilation rates of 40 ach [10]. Also, following the 2003 severe acute respiratory syndrome (SARS) outbreak, case studies indicate cross-ventilation is an effective way of controlling SARS infection in hospitals [11]. However, to date, no one appears to have investigated whether open air retains its lethality to airborne pathogens in hospital wards.

The scientists who coined the term OAF seem to have been unaware of earlier research on fresh air’s germicidal properties [7]. Similar to previous investigators in the field, they were unable to identify what the agent, or agents, involved were. Nevertheless they found that the OAF killed *Escherichia coli*, and also *Brucella suis*, *Staphylococcus epidermidis*, group C streptococcus, *Serratia marcescens* and *Francisella tularensis* [12,13]. Studies with the influenza virus, and Semliki Forest virus, showed that these were also sensitive to the toxic effect of OAF [14,15]. Tests on the influenza virus supported the idea that the risk of catching influenza in a building is far higher than outside [15].

Research into the germicidal properties of open air finished in the 1970s and there was only limited interest in OAF for many years [16]. Recently, one potential component of the OAF has been generated artificially and used to kill airborne pathogens [17–20]. It remains to be determined whether the high natural ventilation rates achievable in pre-1950s hospitals can preserve the OAF indoors. Given the threat to global public health from antimicrobial resistance, influenza, and new, virulent microorganisms, this should be investigated.

Conflict of interest statement

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