Reply to E. Houltz

Sir,

I have read Houltz's letter in response to the paper by Whyte and Lytsy published in the Journal of Hospital Infection and discussing the MRC study of ultraclean ventilation [1, 2]. Before replying to Houltz's criticisms and request for more information, I would like to point out that the object of our article was not to address 'some of the shortcomings of the MRC study'. It was unfortunate that three of four of the main members of the MRC study steering committee retired shortly after the end of the study and misinformation about the study has been frequently published without reply. I thought that information from the remaining member of the steering committee would help to correct this imbalance.

Houltz states that 'This randomization process was, however, not equal at the different hospitals included, but varied between hospitals, and was later approved by the study management'. Unless I have misunderstood what is written, this statement is incorrect. The MRC study was a prospective study with all patients being allotted at random to conventionally ventilated operating theatres or ultraclean air systems by drawing a sealed envelope each week after the operating list had been prepared. However, interpreting what Houltz writes later, he may be referring to the fact that the administration of prophylactic antibiotics was not randomized.

The MRC study was not set up to investigate the effect of prophylactic antibiotics on infections but the effect of ultra-clean air systems. The surgeons were therefore allowed to use antibiotics according to their normal practice and without restrictions. Antibiotic usage was, therefore, equally divided between the ventilation conditions and should, therefore, have little or no effect on the question of whether ultraclean air systems reduced infections after total joint arthroplasty (TJA). Additionally, the results were analysed by multiple regression analysis, a statistical technique used to remove bias from variables connected with the study, including antibiotics, and this showed a reduction of infection rates to be clearly associated with a reduction of airborne microbe-carrying particles (MCPs) [3].

Houltz writes that the amount of MCPs was measured using three different methods and he asks where and when airborne concentrations were obtained in the control and test operating theatres. The concentration of airborne MCPs was measured in all of the operating theatres using the two methods described in the article cited [4]. The type of air sampler used in the UK hospitals was a Casella high volume (700 L/min) slit sampler, with an extension that allowed samples to be taken within 30 cm of the wound. The Swedish centres used Sartorius gelatine membranes in a sterile sampling head that could be placed within 30 cm of the wound. These two methods have been shown to give almost identical results [5]. Four of the hospitals additionally used settle plates exposed close to the wound. Microbiologists were employed to carry out any additional microbiology required for the running of the MRC study and were, therefore, available to carry out extensive air sampling. Sampling varied according to workload, and in some hospitals each operation was sampled but, for example, in Glasgow, where there were additional research commitments, air sampling was carried out one day a week when all TJA operations were sampled; the day of the week was varied to ensure that all consultant surgeons were surveyed.

Houltz enquires whether the observer who judged the type of infection was blinded to the type of ventilation. The observers of infection were part-time research nurses employed by each hospital, and part of their job was to return all information gathered to the MRC statistical unit and to organize the randomization of the patients to the type of ventilation system. They therefore knew which ventilation system was used for each patient but I do not consider that any bias was introduced.

Houltz points out that the patients were followed up for 5 years, with a median follow-up of 2.5 years, but that the loss of patients to follow-up was not mentioned in any of the articles. The loss of patients from follow-up was small, as the MRC study was set up as a prospective study and research nurses were employed to gather information. However, there is no reason to think that follow-up would influence the outcome of the study, as the few patients lost to the study would be equally lost in both the test and control situations.

To more easily understand comments made by Dr Houltz about Table II in our article, which gives the deep joint infection rates obtained by the MRC study in different ultraclean air conditions, the table is reproduced here in Table 1.

Table I Deep joint infection rates after total joint arthroplasty [1

Type of ventilation system	No antibiotics administered	Antibiotics administered
Conventional airflow with conventional clothing	39/1161 (3.4%)	24/2968 (0.8%)
UDAF systems with conventional clothing	8/516 (1.6%)	9/1279 (0.7%)
UDAF systems with total-body exhaust gowns, plus isolators	5/544 (0.9%)	1/1584 (0.06%)

UDAF, unidirectional airflow.

It is pointed out by Houltz that in the group that used conventional clothing as well as prophylactic antibiotics, the infection rate was 0.8% in those operated in conventional air-flow and 0.7% in ultraclean air, and the difference is not statistically significant. However, in a second group where antibiotic prophylaxis was not used, the infection rates were 3.4% in conventional airflow conditions and 1.6% in ultraclean air, and this is significant.

Holtz dismisses consideration of a third group, which had the lowest airborne concentrations and included isolators and UDAF systems with occlusive clothing, as he considers that clothing is ‘really not relevant discussing laminar airflow’. However, the object of the MRC study was not to determine the effect of so-called laminar airflow systems but the effect of ultraclean air, and the study included Allander systems and isolators, as well as occlusive surgical clothing. It is important to understand that occlusive clothing plays a major part in reducing airborne MCPs, and it is necessary to reduce the dispersion of MCPs from the surgical team by occlusive clothing before removing the remaining MCPs by UDAF systems. In this third group, which had the cleanest airborne conditions, the infection rate in patients who received prophylactic antibiotics fell to 0.06%, and when no antibiotics were administered it fell to 0.9%.

It is unfortunate that the decrease in the infection rate owing to ultraclean conditions in the second group of patients was small. However, there are few research studies with perfect results and, taking all the infection rates into consideration, it was the MRC steering committee’s considered opinion that the results were consistent with clean air and prophylactic antibiotics combining independently and multi-plicatively to reduce deep joint infection. It is also important to consider that as well as a simple

comparison of wound infections, a multiple regression analysis was carried out that correlated wound infection rates with other variables that could affect the rates, and these results agreed with the simple comparison [3].

Houltz is critical of Figure 1 which compares the airborne concentration of MCPs during surgery to deep joint sepsis rate. He criticizes the use of a square root conversion in the presentation of the results but we consider this is a reasonable approach, especially if the relationship of wound infection to airborne concentration is not linear. Houltz criticizes our statement that there is a strong correlation between MCP and joint infection and I accept that we have overstated the case. However, in research studies carried out over many years the correlations between airborne microbial concentrations and various sources of contamination usually give poor correlations and, taking this into consideration, I consider this particular correlation to be a reasonable one. Houltz points out the effect of the high outlying result and I accept this had a large effect. However, in many research experiments it is necessary to rely on larger counts which are more accurate. Houltz also criticizes the way results from several hospitals have been combined. However, each hospital had small numbers of infections and it was necessary to combine results from several hospitals with similar airborne concentrations of MCPs. This is a common method of analysing results and avoids the confusing type of result that is shown in the graph that Houltz presents in his letter.

Houltz thinks that one of our criticisms of Bischoff et al.'s study is not justified [6]. It is my opinion that if you wish to compare the infection rate from so-called laminar airflow (LAF) systems with conventional mixed-flow operating theatres you must be confident that the LAF systems produce ultraclean air conditions. Many LAF systems are badly designed and maintained, and this was demonstrated by the survey of 14 hospitals published by Agodi et al., who found that many failed to achieve acceptable average concentrations of $10/m^3$, let alone the desirable $1/m^3$, and some were no better than conventional mixed-flow operating theatres [7]. If you claim that ultraclean air systems do not reduce infection you must demonstrate that the systems called LAF can actually produce low concentrations of airborne MCPs.

Houltz requests that Dr Lytsy and I re-evaluate our conclusion that the results of the MRC study remain 'valid, solid, and convincing'. I accept that not every piece of information reported in the MRC study was perfect but I remain confident that the evidence published by the MRC shows that ultraclean air systems reduce deep wound infection after TJA. However, it is not only the MRC study that is the basis of my conviction. I have no doubt that airborne microbes cause infections in operating theatres [8,9], and in TJA operations more than 90% of the microbes in the wound, before closure, come from the air [4,10]. I am further persuaded by the clinical studies carried out by Charnley [11,12] and the various research studies cited by Bischoff et al. that were not wound registry studies with poor quality results but single hospital studies that showed a decrease in infection rates caused by ultraclean air systems [4]. I also take the common-sense approach that microbial contamination in operating theatres causes wound infections and that an additional reduction of microbial contamination by ultraclean air systems of about 100 times is the way to progress.

I thank Houltz for his diligence in reading our article, as well as affording me a further opportunity to explain parts of the article that were unclear.

References

[1] Whyte W, Lytsy B. Ultraclean air systems and the claim that laminar airflow systems fail to prevent deep infections after total joint arthroplasty. J Hosp Infect 2019; 103:9-15.
[2] Lidwell OM. Air, antibiotics and sepsis in replacement joints. J Hosp Infect 1988; 11(Suppl C):18-40.
[3] Lidwell OM, Lowbury EJL, Whyte W, Blowers R, Stanley SJ, Lowe D. Infection and sepsis after operations for total hip or knee-joint replacement: influence of ultraclean air, prophylactic antibiotics and other factors. J Hyg Camb 1984; 93: 505-29.
[4] Lidwell OM, Lowbury EJL, Whyte W, Blowers R, Stanley SJ, Lowe D. Airborne contamination of wounds in joint replacement operations: the relationship to sepsis rates. J Hosp Infect 1983;4: 111e31.
[5] Parks SR, Bennett AM, Speight SE, Benbough JE. An assessment of the Sartorius MD8 microbiological air sampler. J Appl Bacteriol 1996;80: 529-34.
[6] Bischoff P, Kubilay NZ, Allegranzi Egger M, Gastmeier P. Effect of laminar airflow ventilation on surgical site infections: a system-atic review and meta-analysis. Lancet Infect Dis 2017;17: 553-61.
[7] Agodi A, Auxilia F, Barchitta M, Cristina ML, D'Alessandro D, Mura I, et al. Operating theatre ventilation systems and microbial air contamination in total joint replacement surgery: results of the GISIO-ISChIA study. J Hosp Infect 2015; 90: 213-9.
[8] Ayliffe GAJ, Collins BJ. Wound infections from a disperser of an unusual strain of Staphylococcus aureus. J Clin Path 1967; 20: 195-8.
[9] Payne R. Severe outbreak of surgical sepsis due to Staphylococcus aureus of unusual type and origin. Br Med J 1967; 4(5570):17-20.
[10] Whyte W, Hodgson R, Tinkler J. The importance of airborne bacterial contamination of wounds. J Hosp Infect 1982; 3:123.
[11] Charnley J. Low friction arthroplasty of the hip: theory and practice. Berlin: Springer; 1972.
[12] Lidwell OM. Sir John Charnley, Surgeon (1911e82): the control of infection after total joint replacement. J Hosp Infect 1993; 23:51-5.

W Whyte, University of Glasgow