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EDITORIAL V

Ventilator associated pneumonia: can we ensure that a quality indicator does not become a game of chance?

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Critical care was an early focus of national quality improvement (QI) programmes, driven first by the US-based Institute for Healthcare Improvement (IHI) (http://www.ihi.org) and later adopted in the UK by initiatives such as the Patient Safety First initiative (http://www.patientsafetyfirst.nhs.uk/Content.aspx?path=/interventions/Criticalcare/) and Scottish Patient Safety Programme (http://www.scottishpatientsafetyprogramme.scot.nhs.uk). Much emphasis has been placed on nosocomial infection, of which the most prevalent in the intensive care unit (ICU) is ventilator associated pneumonia (VAP).[1] Ideally, indicators for QI should be person-centred, safe, effective, efficient, equitable, and timely. VAP rates fulfil most of these criteria, because they are relevant to all ICUs, are associated with adverse patient outcomes, and result in greater use of broad-spectrum antibiotics.[1] In principle, measuring VAP rates seems straightforward, does not increase risk to patients, and can be undertaken in all ICUs at low cost.

Various interventions decrease the incidence of VAP when introduced effectively. The quality of evidence for some of these is weak, such as nursing in the head-up position, avoiding frequent ventilator circuit changes, using heat and moisture exchange circuit humidification, and hand-washing, but as these interventions are inexpensive they are strongly

recommended.[1–3] More costly strategies, such as routine oral decontamination with chlorhexidine and the use of sub-glottic suction tubes, are supported by meta-analyses of randomized controlled trials (RCTs), and have therefore also been widely introduced into clinical practice.[4–6] Many ICUs report reductions in the incidence of VAP when these interventions are implemented, usually combined in care bundles. Some healthcare systems are publishing annual national VAP data (http://www.documents.hps.scot.nhs.uk/hai/sshaip/publications/icu-surveillance/icu-annual-report-2012.pdf) and many ICUs report zero VAP rates.[7 8] This is a remarkable achievement given a typical historical incidence of ~20% of admissions.

So is VAP being progressively eradicated? Are there other possible explanations for the impressive reductions in incidence and apparent variation between ICUs? It is important to understand the factors that can influence reported VAP rates to be sure that a potentially robust and relevant QI does not become a game of chance, or worse a metric subject to manipulation. Although national bodies currently emphasize that data should be used to drive local improvement and not necessarily infer differences in quality or safety between organizations, this is a risk as data are made publicly available. In the US mandatory reporting of VAP with penalization of healthcare organizations if cases occur has been extensively debated and is being considered.[9] ICUs that claim or report low or zero VAP rates based on flawed or inaccurate methodology may become complacent, which would offset the intended benefit for patients and healthcare systems.

The National Health Service (NHS) information centre website makes several important statements regarding QIs (http://www.ic.nhs.uk/services/measuring-for-quality-improvement). First is that they are '*assured by clinicians for use by clinicians*'; second is that '*the NHS Information Centre has not applied additional quality assurance to these indicators above that provided by the producing or publishing organisation*.' Together, these statements place a responsibility with the critical care community for ensuring that VAP data are relevant, and the way it is reported is transparent, consistent, and robust.

In addressing these issues, it is useful to consider the evidence that VAP actually worsens patient outcomes, the factors that can influence making a diagnosis of VAP and by inference an ICU's VAP rate, and the non-modifiable risk factors that should be taken into account if VAP rates are compared over time or between different ICUs.

Does VAP actually worsen patient outcome?

VAP is thought to worsen gas exchange, increase sputum load, and potentially result in deterioration of non-pulmonary organ function.[1] These complications are plausible reasons for delayed weaning, prolonged ICU stay, and higher mortality, resulting in greater healthcare costs. Adverse effects may also result from the use of broad-spectrum antibiotics, which are widely used because delayed or inappropriate antimicrobial treatment is associated with poorer outcomes.[1 2] The biological plausibility of these associations is strong, but is difficult methodologically to prove and quantify. Most studies exploring the attributable mortality and morbidity of VAP have used a case controlled or similar observational design. These are all potentially subject to confounding, because a wide range of factors which are difficult to measure or fully quantify during critical illness, and therefore statistically adjust for, increase the risk of both VAP and mortality. A recent systematic review found widely varying attributable mortality from VAP between different observational studies, with an overall estimate of ~27% increased risk.[10] However, a recent large database analysis using complex statistical modelling, incorporating a large number of potential confounders and time effects, concluded that the attributable mortality was only 1–2%.[11] These and similar studies illustrate the limitations of observational designs.[12] They also indicate the likely interplay of multiple factors in determining the importance of VAP between different patients, and also for an individual patient at different stages of their critical illness. The attributable mortality of VAP from multi-drug resistant (MDR) bacteria is also almost certainly higher than for more sensitive organisms, indicating 'not all VAP is the same'.

The other more robust way to examine effects on mortality and other patient outcomes is to examine data from RCTs of interventions that decrease VAP. The primary outcome in these trials was usually VAP rate, so most are underpowered for secondary outcomes such as length of stay and mortality. A recent systematic review identified 58 randomized comparisons of interventions intended to reduce VAP, of which 20 caused significant reductions in the RCT.[13] Although no mortality difference was demonstrated in any individual study, the pooled estimates suggested an attributable mortality from VAP of ~10%, but with wide variation between studies.

Taken together, the available data are consistent with a real if difficult to quantify direct link between VAP and excess mortality, and by inference other adverse effects. However, given the limited external generalizability of much of the published evidence, the key message is perhaps that demonstrating a reduced VAP rate should not be assumed to be reducing mortality, length of stay, or antibiotic use unless these are actually measured as part of the QI process.

What factors influence making the diagnosis of VAP?

Diagnosing VAP is not straightforward. Many would argue that the gold standard is lung biopsy or post-mortem examination, which are rarely available.[1 2] There is no universally agreed clinical definition and those in widespread use differ in their complexity. In general terms, definitions designed for clinical surveillance use a mixture of clinical and radiological symptoms and signs. The three most widely used definitions are those of the American College of Chest Physicians,[14] the Centers for Disease Control (CDC) National Healthcare Safety Network (http://www.cdc.gov/HAI/vap/vap.html) (both North American) and the Hospitals in Europe Linked for Infection Control through Surveillance project (http://helics.univ-lyon1.fr/protocols/icu_protocol.pdf) (Table 1). Many healthcare surveillance systems will use these clinical definitions to screen for

VAP because they are perceived as simple, and do not require or mandate microbiological confirmation. However, the definitions are different and fields within all three are semi-subjective. For example, chest radiographs are frequently abnormal in ventilated patients, many of whom have acute lung injury, such that judging new or progressive changes is significantly reviewer dependent. Tejerina and colleagues[15] showed that agreement between intensivists was low (κ statistic 0.47) when asked to ascertain the presence of changes consistent with VAP. It is also relevant that chest radiography needs to be performed to make a diagnosis, whereas daily chest imaging is unusual in many ICUs and the overall frequency of chest X-rays has decreased substantially in recent years. Other fields, such as the presence of purulent secretions, altered mental status, and changes in chest signs are also subjective. The introduction of subjectivity to diagnosis is a potential source of ascertainment bias, especially when the outcome has connotations of poor quality. Systematic bias may also be introduced depending on the professional undertaking screening, which can include medical staff, infection control professionals, or staff trained specifically in surveillance. For example, Thomas and colleagues[16] observed VAP rates of 28% in an ICU when ICU staff screened, whereas surveillance staff documented rates of 8% for the same patient cohort. Similarly, Skrupky and colleagues[17] compared rates when surveillance staff used the National Healthcare Safety Network definition with simultaneous screening using the ACCP definition done by medical staff. Over a 1-yr period surveillance staff reported an annual VAP rate of 1.2 cases per 1000 ventilator days, whereas medical staff reported 8.5 per 1000 ventilator days for the same 2060 patients. Agreement between the two methodologies was extremely poor (κ statistic 0.26) despite similar proportions of patients having microbiology positive VAP. Even within the same professional group agreement may be limited; a study comparing specialist surveillance staff found rates ranging from 20 to 40% with very poor agreement.[18] These issues could clearly explain potentially large variation in VAP rate creating uncertainty regarding the relative importance of quality of clinical care *vs* methodological bias. A recent comparative study of 47 US trauma centres reported

Table 1 A comparison of the American College of Chest Physicians, the CDC National Healthcare Safety Network, and the Hospitals in Europe Linked for Infection Control through Surveillance project (HELICS) clinical definitions of VAP

Definition	Radiological criteria	Clinical criteria	Chest signs
American College of Chest Physicians (Pingleton and colleagues[14])	New or progressive consolidation on chest radiographs	**AND** At least **two** of the following: Fever >38°C **OR** White cell count of >12 000 mm^{-3} or <4000 mm^{-3} **OR** Purulent secretions	
CDC National Healthcare Safety Network (http://www.cdc.gov/HAI/vap/vap.html)	Two or more serial radiographs with at least one of the following: New or progressive and persistent infiltrate OR Consolidation OR Cavitation	**AND** at least one of the following: Fever >38°C **OR** White cell count of >12 000 mm^{-3} or <4000 mm^{-3} **OR** For adults ≥70-yr old, altered mental status with no other recognized cause	**AND two** of the following: New onset of purulent sputum or change in character of sputum or increased respiratory secretions or increased suctioning requirement **OR** New onset or worsening cough or dyspnoea, or tachypnoea **OR** Rales or bronchial breath sounds **OR** Worsening gas exchange (e.g. oxygen desaturations, increased oxygen requirements, or increased ventilator demand)
Hospitals in Europe Linked for Infection Control through Surveillance project (HELICS) (http://helics.univ-lyon1.fr/protocols/icu_protocol.pdf)	A chest X-ray or computed tomography scan suggestive of pneumonia (two or more required for patients with underlying cardiac or pulmonary disease)	**AND** at least one of the following: White cell count of >12 000 mm^{-3} **OR** <4000 mm^{-3} **OR** Temperature >38°C with no other cause	**AND** at least **one** of the following **(two required if microbiology is by qualitative tracheal aspirate culture or if culture is negative)**: New onset of purulent sputum or change in character (colour, odour, consistency, or quantity) **OR** Cough, dyspnoea, or tachpnoea **OR** Auscultatory findings (rales, bronchial breathing, rhonchi, and wheeze) **OR** Worsening gas exchange (e.g. desaturation, increasing F_{IO_2}, or ventilation requirements)

VAP rates ranging from 1.8 to 57.6 per 1000 ventilator days.[19] Variation was not explained by differences in injury severity, diagnostic methodology, or hospital size, but was strongly associated with the staff group undertaking surveillance. Rates were highest when trauma service staff was responsible for VAP ascertainment (26.4%), lowest for surveillance staff (11.3%), and intermediate for mixed models (18.9%).

Clinical definitions for VAP tend to have high sensitivity, at the expense of lower specificity (high false positive; low false negative rate), simply because a variety of non-infective aetiologies satisfy each of the definitions of 'VAP' listed in Table 1. VAP detected using these surveillance systems are more appropriately called 'clinically suspected VAP'. One way to increase specificity is to include microbiological confirmation in the diagnosis. This allows VAP rates to be described in terms of clinically suspected rates, microbiologically confirmed VAP or both. This approach still requires consistent recognition of possible VAP based on clinical criteria and is more labour intensive, but has the potential to reduce variability attributable to methodology and observer error. However, systematic differences are introduced by the microbiological methods used, which each have different sensitivity and specificity. For example, non-quantitative culture of tracheal aspirate (TA) will have higher positivity than semi-quantitative culture of a bronchoalveolar lavage (BAL).[1] Morris and colleagues[20] used paired TA and BAL samples to estimate the specificity of TA compared with BAL as only 14%, and showed that the choice of diagnostic microbiological sample could theoretically result in four-fold differences in reported VAP rate even when only microbiologically confirmed cases of VAP were reported. As part of a QI programme, they further showed that increasing the proportion of clinically suspected VAP investigated by BAL from 37 to 58% over time within their ICU resulted in a halving of reported microbiologically confirmed VAP despite rates of clinical diagnosis being unchanged. This observation is perhaps unsurprising because pneumonia, by definition, affects the gas exchanging regions of the lung (which are sampled by good quality BAL) whereas TA is likely to reflect secretions from the conducting airways.

These issues clearly show the multiple factors influencing a reported VAP rate, many of which might not reflect differences in quality of care or, by implication, patient outcomes. The potential for methodological issues to introduce both random error and systematic bias creates major uncertainty in relation to the NHS Information Centre's intention that a QI should be quality assured by clinicians themselves or their organizations. This loud 'noise' around the measurement of VAP rates emphasizes the need to track other relevant outcomes, such as antibiotic exposure, duration of ventilation, and trends in standardized mortality rates. For example, Morris and colleagues[21] showed that the introduction of a VAP prevention bundle using IHI methodology (oral chlorhexidine, 'wake and wean', $>30^{\circ}$ head-up position) resulted in a decrease in both clinical and microbiologically confirmed VAP rates, which was also associated with reductions in antibiotic use, ICU length of stay, and mortality among patients requiring ≥ 6 days of mechanical ventilation. Demonstrating concurrent improvements in patient-centred outcomes improves internal validity, justifies the effort invested in the QI process, and makes comparisons between ICUs less 'threatening' to organizations. It is also a means of continuing to drive QI when VAP rates are low or even zero.

What factors should be taken into account when comparing VAP rates between ICUs?

The issues set out above clearly indicate the importance of diagnostic methodology and process, but in order to provide meaningful comparisons over time within an ICU, or compare different ICUs, other factors relating to case mix also need to be considered. For example, a range of non-modifiable patient factors have been shown to increase the subsequent risk of VAP, including chronic lung disease, dialysis-dependent renal failure, immunosuppression, prior antibiotic exposure, long-term residential accommodation, and prolonged pre-ICU hospital stay.[1] In addition, the local prevalence of MDR pathogens and rates of colonization at ICU admission will further modify the risk of acquiring VAP. Once admitted to the ICU, the cumulative risk of VAP for an individual patient is closely related to the duration of mechanical ventilation. This

Table 2 Questions to address when reporting VAP rates that will increase both internal and external validity and enable more meaningful comparisons within and between ICUs

Structure
• What is the case mix of the ICU?
• Are there a high proportion of 'high risk' groups for VAP, for example immunosuppressed patients?
• What is the median length of stay of patients?
• How many and what proportion of patients require longer periods of ventilation, for example, ≥ 7 days and ≥ 14 days?
Process
• Which staff members undertake HAI surveillance?
• What consistency and quality checks are in place locally in relation to screening?
• Who is responsible for triggering clinical suspicion of VAP, interpreting X-rays and clinical signs, and ascertaining diagnosis?
• What microbiological techniques are used for VAP investigation, and what proportion of suspected VAP is investigated with each?
• What criteria are used to report a positive VAP: clinical criteria alone or clinical plus positive microbiology?
Outcome
• How many antibiotics are used in the ICU and have these changed in parallel with VAP rates, for example mean antibiotic days per admission?
• What are the duration of mechanical ventilation, ICU stay, and ICU/hospital mortality and have these changed in parallel with VAP rates?
• Have these outcomes changed for the highest risk sub-groups, for example cohorts requiring ≥ 7 days of mechanical ventilation or immunosuppressed patient cohorts?
• Has the incidence of MDR infection, methicillin resistant Staphylococcus aureus (MRSA), or *Clostridium difficile* changed in parallel with VAP incidence?

means that ICUs treating higher numbers of patients requiring longer periods of mechanical ventilation have a non-modifiable risk of higher VAP rates. Differences may be further magnified by the current standard reporting methodology of rates per 1000 ventilator days, which is sensitive to neither illness severity nor patterns of ventilation. An ICU treating 500 mainly post-surgical patients annually with a mean ventilation time of 3 days will use the same denominator as an ICU treating 250 medical patients with a mean ventilation time of 6 days, but the individual patient risk for the second ICU is substantially higher. These issues may explain why higher VAP rates are likely in larger ICUs with a more complex case mix, even when staffing, protocols, and preventive strategies are similar.[22]

In conclusion, it is clear that VAP is a relevant QI, but only if its internal and external validity is fully understood. Current methodologies are not fit for purpose to make comparisons between ICUs without describing the methodologies used, their precision, and the case mix to which they apply. In taking forward this quality agenda we suggest including information with VAP incidence reports about several structure-, process-, and outcomes-related issues both within institutions, and particularly when comparing VAP rates between ICUs. These are listed in Table 2. Addressing these issues will ensure that the quality agenda within ICUs builds on the tremendous progress made and is taken to the next level. In this way, we can ensure that VAP rates and similar measures continue to work to our patients' benefit, remain credible to clinicians, and do not become metrics subject to manipulation or penalization.

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