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Short communication

Use of surveillance data to calculate the sample size and the statistical power of randomized clinical trials testing *Staphylococcus aureus* vaccine efficacy in orthopedic surgery

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ABSTRACT

Background: Patients undergoing primary total hip arthroplasty (THA) would be a worthy population for anti-staphylococcal vaccines. The objective is to assess sample size for significant vaccine efficacy (VE) in a randomized clinical trial (RCT).
Methods: Data from a surveillance network of surgical site infection in France between 2008 and 2011 were used. The outcome was *S. aureus* SSI (SASSI) within 30 days after surgery. Statistical power was estimated by simulations repeated for theoretical VE ranging from 20% to 100% and for sample sizes from 250 to 8000 individuals per arm.
Results: 18,688 patients undergoing THA were included; 66 (0.35%) SASSI occurred. For a 1% SASSI rate, the sample size would be at least 1316 patients per arm to detect significant VE of 80% with 80% power.
Conclusion: Simulations with real-life data from surveillance of hospital acquired infections allow estimation of power for RCT and sample size to reach the required power.

1. Introduction

Staphylococcus aureus (*S. aureus*) is a leading cause of healthcare-associated infections (HAI) in conjunction with high mortality [1] which is due to antibiotic resistance and multiple virulence factors [2]. *S. aureus* is 1 of 3 major causes of surgical site infection (SSI) and is frequently isolated from infected surgical sites in orthopedics [3]. *S. aureus* SSI (SASSI) may induce an increase in hospital length of stay of 12 days [1] and cases caused by MRSA resulted in an attributable excess of costs and length of stay of 23 days in the USA [4]. With time, antibiotic prophylaxis promotes the development of methicillin-resistant *S. aureus* (MRSA) [5]. A *S. aureus* vaccine would be contributive for prevention. However, prophylactic *S. aureus* vaccine development remains challenging [6,7]. To date, clinical trials have failed to demonstrate vaccine efficacy (VE) in patients at high risk of SSI, such as those undergoing cardiothoracic surgery [8] or hemodialysis [9,10].

The population of patients undergoing primary total hip arthroplasty (THA) with a SASSI incidence of 0.35% was most likely to gain from vaccination as previously reported [11]. Patel et al. [12] reported SASSI incidence ranging from 0.18% to 3.8% in 81 studies of patients undergoing hip arthroplasty. These rates seemed to be moderate, but the annual number of THAs doubled between 2000 and 2010 in the USA – from 138,700 in 2000 to 310,800 in 2010 [13] and reached 329,766 in Europe in 2013–2014 [3]. THA numbers are expected to continue increasing as the population ages and adults live longer. The impact of an efficient vaccine on public health could be significant.

Abbreviations: SSI, surgical site infection; SASSI, *Staphylococcus aureus* surgical site infection; *S. aureus*, *Staphylococcus aureus*; THA, total hip arthroplasty; VE, vaccine efficacy; MRSA, methicillin-resistant *S. aureus*; HAI, hospital acquired infections.

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In vaccine trials, some concerns remain about whether the number of events being observed in the study would be sufficient to establish vaccine superiority and, finally, support vaccine licensure. Given their high cost, phase III studies must be powered to estimate an effect with moderate significance. If an effect is evident, the trial could be expanded.

The objective is to estimate, by simulation, the sample size required for evidence of significant VE in a potential clinical trial of primary THA based on standardized surveillance data.

2. Methods

2.1. Population

Patients included were hospitalized for THA in wards of South-East of France participating in the national SSI Surveillance Network between 2008 and 2011 [http://cclin-sudest.chu-lyon.fr/Reseaux/accueil.html, [14]].

The outcome was SASSI occurrence within 30 days after THA. Analysis was restricted to patients older than 50 years. Cases with American Society of Anesthesiologists (ASA) score of 5 (classified as moribund) were excluded, as were cases infected by agents other than *S. aureus* and cases with missing data. Potential SASSI risk factors were evaluated by estimating SASSI relative risk (RR) not adjusted and adjusted for gender, age, ASA score, and type of surgical procedure (simple or multiple). Poisson linear regression was undertaken.

2.2. Statistical power analysis

2.2.1. Simulations with SASSI rate observed from real-life data

The 2 groups of randomized patients (vaccine vs control) were balanced by risk factors known before surgery and highlighted in the data [15]. Male gender, high ASA score (“>2” compared to “1–2”) and multiple procedures were associated with higher SASSI (Table 1). Only gender and ASA score were retained for stratification, to have a sufficient number of infected patients per stratum.

The 2 patient groups stratified by gender and ASA score, were then sampled with replacement 5000 times. In the virtually-vaccinated group, infection status was drawn from binomial distribution, with number of infected patients observed in this group and theoretical VE as parameters to determine which infected patients would have become still infected even if they had been vaccinated. The RR of infection in the vaccinated group was estimated by Poisson regression adjusted for gender and the National Nosocomial Infection Surveillance (NNIS) risk index only known after surgery. RR two-tailed *P*-values indicated whether the vaccination effect on infection was significant at 5%. Estimated VE was derived from the RR of infection by the formula 1-RR. Simulations were repeated for theoretical VE, ranging from 20% to 100% by stepwise increments of 20% and for 6 sample sizes ranging from 250 to 8000 individuals per arm.

The proportion of positive, significant vaccination effects, given theoretical VE and sample size, estimates statistical power for this virtual trial, i.e., the probability of significant vaccine effect, given its theoretical VE with a given sample size.

2.2.2. Simulations using real-life data with fixed expected SASSI rate

A second series of simulations was performed by fixing expected SASSI rate at 1, 2 and 4% in each arm. The observed number of infected patients in both groups was drawn from binomial distribution with sample size and expected SASSI rate as parameters. Then, observed infected and non-infected subjects were randomly selected among infected and non-infected populations, respectively. In the virtually-vaccinated group, infection status of the observed infected patients was drawn from binomial distribution, with number of infected patients observed in this group and theoretical VE as parameters. Simulations were repeated for theoretical VE of 20%, 40% and 80%, leading to 9 combinations (SASSI rate, VE).

Statistical power was then computed, for each combination of VE, sample size and expected SASSI rate. Sample size for statistical power of 20%, 40% and 80% was then predicted for each combination (SASSI rate, VE) using regression of sample size on computed statistical power.

3. Results

A total of 18,688 patients >50 years and undergoing THA were included (Supplementary Figure 1). Mean age was 72 years (±10), and 58% were women. Sixty-six (3.5‰) SASSI occurred (Table 1). Gender, NNIS risk index and type of surgical procedure had significant effects on SASSI.

3.1. Simulations with SASSI rate from real-life data

Table 2 reports the statistical power evidencing vaccine effects, given different theoretical VEs and sample sizes. To be able to evi-

Table 1
Characteristics of patients undergoing primary total hip arthroplasty included in the study.

		Without SASSI (n%)	SASSI (n%)	Not adjusted RR SASSI (95% CI)	Adjusted RR SASSI (95% CI)
	n	18,622	66		
Gender					
	Female	10,768 (57.8)	26 (39.4)	1 (Ref.)	1 (Ref.)
	Male	7854 (42.2)	40 (60.6)	2.10 (1.28–3.45)*	2.09 (1.26–3.46)*
Age (year old)	mean ± SD	72.6 ± 10	73 ± 11.1		
Age categories					
	50–59	2294 (12.3)	10 (15.2)	1 (Ref.)	1 (Ref.)
	60–69	4881 (26.2)	16 (24.2)	0.75 (0.34–1.66)	0.79 (0.36–1.74)
	70–79	6644 (35.7)	18 (27.3)	0.62 (0.29–1.35)	0.61 (0.28–1.35)
	80+	4803 (25.8)	22 (33.3)	1.05 (0.5–2.22)	0.88 (0.4–1.93)
ASA score					
	1–2	13,660 (73.4)	32 (48.5)	1 (Ref.)	1 (Ref.)
	>2	4962 (26.6)	34 (51.5)	2.91 (1.8–4.72)*	2.79 (1.68–4.64)*
Type of surgical procedure					
	Simple	18,239 (97.9)	61 (92.4)	1 (Ref.)	1 (Ref.)
	Multiple	383 (2.1)	5(7.6)	3.87 (1.55–9.62)*	3.55 (1.42–8.89)*

* $P \leqslant .05$: Poisson regression model.

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