Fast Tracking the Vaccine Licensure Process to Control an Epidemic of Serogroup B Meningococcal Disease in New Zealand

Diana Lennon,1 Catherine Jackson,1,a Sharon Wong,1,a Maraekura Horsfall,1,a Joanna Stewart,2 and Stewart Reid3,4
1Community Paediatrics, 2Epidemiology and Biostatistics, and 3Immunisation Advisory Center, The University of Auckland, and 4Ropata Village Medical Centre, Lower Hutt, New Zealand

Epidemics of serogroup B meningococcal disease are rare. Strain-specific outer membrane vesicle vaccines, which are not marketed, are the only current tool for control. A correlate of protection is ill defined, but published data suggest that measured serum bactericidal antibody levels parallel efficacy. Even infants can mount a strain-specific antibody response to a strain-specific vaccine. New Zealand’s epidemic (1991–2007; peak rate [in 2001], 17.4 cases per 100,000 persons) was dominated by a single strain. After a 5-year search (1996–2001) for a manufacturer for a strain-specific outer membrane vesicle vaccine, a fast-tracked research program (2002–2004) determined the safety and immunogenicity of vaccine in infants (2 age groups: 6–10 weeks and 6–8 months), children (age, 16–24 months), and school-aged children (age, 8–12 years) after an adult trial. The vaccine was reactogenic, compared with control vaccines (meningococcal C conjugate and routine infant vaccines), but retention was high. Three vaccine doses produced antibody levels (measured by serum bactericidal assay) that were considered to be adequate for public health intervention. However, in young infants, a fourth dose was required to achieve levels equivalent to those achieved by other age groups. Provisional licensure by New Zealand’s MedSafe was based on serological criteria strengthened by bridged safety data from studies of the parent outer membrane vesicle vaccine, independent assessment of manufacturing quality, and a clear plan for safety monitoring and effectiveness evaluation after licensure.

To facilitate the control of an epidemic of single-strain dominated serogroup B meningococcal disease in New Zealand (NZ), licensure of a tailor-made strain-specific outer membrane vesicle (OMV) vaccine was based on serologic criteria alone with bridged safety data from the parent vaccine without direct evidence of efficacy. This is a collation of published data on this process.

Neisseria meningitidis is a leading cause of bacterial meningitis and other invasive bacterial infections worldwide [1–3]. Endemic serogroup B meningococcal disease accounts for a substantial proportion of cases of meningococcal disease in the United States and other developed countries and accounts for approximately one-half of invasive meningococcal disease in infants in the United States [1]. Epidemics of serogroup B disease have occurred in many parts of the world [4–7].

Because outbreaks of serogroup B meningococcal disease tend to be clonal, the development of OMV vaccines that target the outbreak strain has been possible. These vaccines are not commercially available.

Beginning in 1991 (figure 1), NZ experienced an outbreak of serogroup B disease; 86% of cases (during 1990–2003) were caused by the B:4:P1.7–2,4 strain [8–10]. Expression of the P1.7–2,4 PorA gene served as a marker of the ST-41/44 clonal complex [10]. Surveillance of meningococcal disease in NZ entails a combination of notification and laboratory data reconciled at the national level [11]. The relative stability of the epidemic strain PorA protein supported the use of a strain-specific OMV vaccine for epidemic control [12].

The epidemic peaked in 2001 (rate of notified disease, 17.4 cases per 100,000 persons per year; rate of disease due to the...
VACCINES

To date, vaccines evaluated in detail for serogroup B meningococcal disease have been outer membrane protein vaccines [25, 26]. Protection against meningococcal disease has been demonstrated to correlate with bactericidal antibodies [27], but in serogroup B infections, bactericidal antibodies are directed against noncapsular surface antigens [28, 29]. Evidence of involvement of outer membrane proteins (especially PorA) in immunity is accumulating [30–32]. However, unlike serogroup C meningococcal disease, no clear correlate of protection is known [33–35]. Studies evaluating age-specific serum bactericidal activity in parallel with field efficacy estimates in Brazil and Chile support the use of serum bactericidal activity as a correlate of protection [16, 30, 36]. A landmark Chilean study involving infants and children that was performed in 1996 demonstrated excellent activity against the strain against which the infants and children had been vaccinated but had no activity against other strains [37]. This led to NZ’s decision to use a “designer” vaccine to control an epidemic that occurred largely among young children and that was dominated by a single strain. The search for a vaccine manufacturer took 6 years (1996–2001). A public–private partnership (2002–2006) was forged between Chiron Vaccines (now Novartis) and the NZ Ministry of Health, with technology transfer from the Norwegian Institute of Public Health (NIPH).

Evaluation of the efficacy of OMV vaccines has been dogged with inconsistencies. Efficacy was established in older children in 2 randomized controlled trials [5, 38]. Rapid decrease of vaccine-induced antibody responses in the Norwegian 2-dose trial led to efficacy results of 57% after 29 months [5]. A later estimated efficacy of 87% at 10 months suggested potential short-term usefulness of this vaccine [39]. To ameliorate the rapid decrease in antibody levels, a third or fourth dose was studied in additional trials [37, 39–42]. The proven efficacy of OMV vaccines in children aged <5 years was unclear [6, 7, 36, 38, 43, 44].
NZ’S APPROACH

In the face of a well-characterized, ongoing epidemic dominated by a single strain of meningococcus, a rapid clinical development plan (figure 5) was evolved to estimate immunogenicity, safety, and reactogenicity. After production of a vaccine based on the NZ epidemic strain by NIPH and enrollment of health care adult volunteers in a phase I/II trial, trials involving children aged 8–12 years, 16–24 months, 6–8 months, and 6–10 weeks followed in quick succession. Trials proceeded in school children as soon as the NZ strain vaccine was known to be immunogenic and not to be associated with serious adverse events in adults (n = 49). Similarly, a small trial to confirm safety in adults (n = 10) was performed using the Chiron-produced NZ strain vaccine after technology transfer from NIPH before the trial of this product in school children and was followed by a trial involving infants aged 6–10 weeks. Approximately 1500 participants were enrolled into clinical trials over ~24 months. Supported by the knowledge that measurable antibodies parallel efficacy and to facilitate rapid progress to licensure and epidemic control, a randomized efficacy trial was omitted.

A number of elements were considered to be essential for licensure of the NZ meningococcal OMV vaccine (MeNZB) without a phase III efficacy trial to support the licence application. These elements included a well-characterized clonal outbreak [10], leading to the development of a strain-specific OMV vaccine; the assumption that serum bactericidal antibody measurements are likely to reflect potential vaccine effectiveness, with an increase in antibody titer (as opposed to absolute titer cutoff) being a reasonable approach in the absence of a clear-cut correlate of protection [16, 30]; proven efficacy by randomized controlled trial of OMV vaccines in older children [5, 38], including the Norwegian parent vaccine (strain: B:15:P1.7,16), an OMV vaccine previously developed by NIPH; standardization of the serum bactericidal assay across 3 laboratories (led by NZ) [45]; ≥3 vaccine doses shown to produce antibody levels considered to be adequate for public health intervention age groups, as measured by serum bactericidal assay; and randomized controlled trial safety data from other OMV vaccines, including the NIPH parent vaccine (171,800 students aged 14–16 years) [16, 38, 46]. A study from Chile used purified outer membrane protein strain-specific vaccine in a randomized controlled trial design involving 40,800 participants [16]. The Cuban randomized controlled trial involved 106,400 students aged 10–14 years and used a strain-specific (B:4:P1.15) OMV vaccine mixed with a C polysaccharide vaccine [38]. Other elements essential for licensure were reactogenicity and immunogenicity data, by age group, available from other published trials [16, 37, 39, 46]; reactogenicity and immunogenicity data, by age group, available from the NZ trials of the NZ OMV vaccine [17–22] (the size of these trials was increased beyond the size needed to demonstrate immunogenicity, to produce more reactogenicity data); and manufacturing quality, as overviewed independently by the National Institute of Biological Standards (United Kingdom), which allowed safety data from NIPH (parent) vaccine studies to be bridged to support the NZ vaccine.

NZ OMV vaccine (MeNZB) safety monitoring was pre-planned postlicensure, as required for licensure [47]. Before the MeNZB initiative, vaccine safety surveillance in NZ was solely a standard passive reporting system conducted by the Centre for Adverse Reaction Monitoring. There was no national immunization register. The prelicensure safety database comprised ~3300 doses. A comprehensive phase IV safety monitoring system (Meningococcal Vaccine Safety Strategy, Data Management

<table>
<thead>
<tr>
<th>Variable</th>
<th>6–10 weeks</th>
<th>6–8 months</th>
<th>16–24 months</th>
<th>8–12 years (cohort A)</th>
<th>8–12 years (cohort B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%) of seroresponders [95% CI]a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After dose 3c</td>
<td>239 (53) [46–59]</td>
<td>163 (74) [68–80]</td>
<td>254 (75) [69–80]</td>
<td>220 (74) [67–79]</td>
<td>230 (79) [73–84]</td>
</tr>
<tr>
<td>After dose 4d</td>
<td>45 (69) [54–80]</td>
<td>...</td>
<td>42 (100) [90–100]</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>No. (%) of participants with a titer ≥1:4 [95% CI]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After dose 3c</td>
<td>239 (76) [70–81]</td>
<td>202 (92) [88–95]</td>
<td>254 (92.2) [88–95]</td>
<td>224 (92) [88–95]</td>
<td>230 (95) [91–97]</td>
</tr>
<tr>
<td>After dose 4c</td>
<td>45 (82) [68–91]</td>
<td>...</td>
<td>42 (100) [90–100]</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

NOTE. Data are from [17, 18, 20–22]. CI, confidence interval.

a Current notation: P1.7–2,4.
b Seroresponders were defined as participants who had a ≥4-fold increase in serum bactericidal antibody titer, compared with prevaccination baseline interpolated titers. A baseline titer of <1:4 was required to reach a titer of ≥1:8 (seroresponse).
c Four to 6 weeks after administration of a vaccine dose.
d The fourth dose was given 5 months after dose 3.
e For the infants aged 16–24 months who seroresponded to a 3-dose priming series, the fourth dose was given 17 months after dose 3. For 30 children aged 16–24 months who did not serorespond to a 3-dose priming series, the fourth dose was given 11 months after dose 3 and resulted in seroresponse in 100% (86%–100%) and in a titer ≥1:4 in 100% (86%–100%).
Figure 2. Interpolated antibody titers to New Zealand (NZ) strain (NZ98/254) in participants vaccinated with 3 doses of NZ strain outer membrane vesicle (OMV) vaccine (MeNZB), as measured by serum bactericidal assay (intention-to-treat analyses) [17–22]. Boxplot was plotted on the log 2 scale. The box represents the interquartile range, the center line represents the median, the black dot represents the mean values, and circles represent the individual values beyond the whiskers, which extend to the last value within 1.5 times the interquartile range. Blood samples were obtained at 4–6 weeks after administration of a vaccine dose. The trials for persons aged 8–12 years were run in 2 cohorts (A and B) at different times. Cohort A received the Norwegian Institute of Public Health-produced NZ strain OMV vaccine at 0, 5, and 12 weeks, and cohort B and infants received the Chiron (now Novartis) NZ strain OMV vaccine at 0, 6, and 12 weeks. Among infants aged 6–10 weeks, after 4 doses of MeNZB, the geometric mean titer increased to 21.3 (95% confidence interval, 12.3–36.7).

Group 2004) was required. The key features of this system [48] were establishment of a National Immunization Register; use of several data sources comprising several elements (the existing passive reporting system, an intensive vaccine monitoring program in which all clinical events were reported to Centre for Adverse Reaction Monitoring for a 6-week period after vaccination [49], and hospital based monitoring [described below]); separation of data collection and analysis from data assessment (an independent safety monitoring board [ISMB] was established by the NZ Health Research Council to assess all safety data); staggered progress of the vaccination campaign, which required that the ISMB assess predetermined safety datasets to permit progressive extension of the vaccination campaign from the highest-risk areas offered immunization to the rest of the country; and hospital-based monitoring, based on the Canadian Impact system [50]. This was established by 4 district health boards considered to be at highest risk of disease and involved monitoring of hospitalizations for ~200,000 vaccinees and ~600,000 vaccine doses. A list of adverse events possibly attributable to meningococcal OMV vaccine administration was established from experience with other OMV vaccines and was expanded to include other vaccine-related adverse events (e.g., neurological symptoms). A priori determined case definitions and background disease rates were established. Nurse monitors screened admission lists daily for events of interest and reported to a clinical review committee of pedi- atricians to aid interpretation. A cluster investigation protocol was available.

Vaccine effectiveness evaluation was preplanned postlicen-sure [44, 51–53]. In the absence of a population-based ran-
Figure 3. Persistence of immune response geometric mean titers, as measured by serum bactericidal assay, against the vaccine strain NZ98/254 in participants vaccinated with the New Zealand (NZ) outer membrane vesicle (OMV) vaccine (MeNZB) [18]. Top, Titers in persons aged 8–12 years (62 in cohort A [black] and 91 in cohort B [white]). Bottom, Titers in infants (gray) aged 6–8 months (n = 40). Squares indicate geometric mean titers, circles indicate median values, and whiskers indicate interquartile ranges. Cohort A received the Norwegian Institute of Public Health–produced NZ strain OMV vaccine at 0, 5, and 12 weeks, and cohort B and infants received Chiron (now Novartis) NZ strain OMV vaccine at 0, 6, and 12 weeks.

Figure 4. Geometric mean serum bactericidal antibody titers after administration of 3 doses of meningococcal conjugate vaccine (MCC; three 10–μg doses were given at 2, 3 and 4 months of age [23]), New Zealand outer membrane vesicle (OMV) vaccine (MenZB; 3 doses were given at 6 weeks, 3 months, and 5 months of age; serum bactericidal antibody titer against the vaccine strain NZ98/254 [22]), or recombinant meningococcal B vaccine with NZ98/254 OMV (rMenB + OMV; 3 doses given at 2, 4, and 6 months of age; serum bactericidal antibody titer against the vaccine strain NZ98/254 [24]) in infants. Error bars show the 95% confidence interval of the geometric mean titer and not the distribution of serum bactericidal antibody titers.

domized controlled trial of vaccine efficacy of the MeNZB vaccine, application to the licensure authority included a postlicensure effectiveness evaluation. A suite of observational methods included disease surveillance, modeling of effectiveness, and a case-control study of vaccine effectiveness. The staged vaccine delivery throughout NZ allowed regression modeling techniques using current and historical data to evaluate the effectiveness of the program, reducing confounding by the natural epidemic path. A case-control study of vaccine effectiveness among children aged <5 years was planned, because it could reduce confounding influences. Funds were withdrawn for this 2-year study after the first year.

NZ’s legislation allowing “license with provisional consent” [54] in special circumstances, such as an epidemic, was a key element. Earlier licensure decisions made in other jurisdictions on the basis of immunologic data alone were noted (influenza vaccines annually, quadrivalent polysaccharide meningococcal vaccines, and the experience in the United Kingdom with conjugate serogroup C meningococcal vaccines) [55].

IMMUNOLOGIC ASSESSMENT OF MENZB

Early discussion between the manufacturer and Medsafe indicated that the licensure of the NZ strain vaccine (MeNZB) would be considered on the basis of immunogenicity data and age group, without direct evidence of efficacy. Because the correlate of protection was uncertain, a threshold of antibody titer increase that was acceptable for vaccine use in epidemic control was agreed upon before commencement of the trials (see next paragraph). An outline of this strategy was peer reviewed internationally and nationally before the trials commenced [56].

The primary immunogenicity outcome measure for all trials was an serum bactericidal antibody response against N. meningitidis serogroup B strain NZ98/254 (the vaccine strain). Seroresponse was defined as a ≥4-fold increase serum bactericidal antibody titer from that measured before vaccination, with an increase to at least 1:8 if the prevaccination titer was <1:4 [20]. Studies had 80% power for the lower 95% confidence limit of seroresponders being ≥40%, given a true value of at least 50% (the agreed minimum acceptable threshold). The studies also
Seroresponders (R) were defined as those who had a 4-fold increase in serum bactericidal antibody titer, compared with prevaccination baseline interpolated titers. A baseline titer of <1:4 was required to reach a titer of ≥1:8 (seroresponse). A, cohort A, for which the Norwegian Institute of Public Health–produced New Zealand strain outer membrane vesicle vaccine was used; B, cohort B, in which Chiron (now Novartis)–produced New Zealand strain outer membrane vesicle vaccine was used; NR, nonresponder.

Randomized, controlled, observer-blinded trials were conducted in Auckland with use of 3 doses of 25 μg of MeNZB administered intramuscularly 6 weeks apart; doses were added in extension studies (table 1, figure 2, and figure 3). Timing of administration for very young infants was in accordance with the NZ infant immunization schedule (at 6 weeks, 3 months, and 5 months of age).

In a phase I/II trial involving adults, there was a 4-fold increase in antibody titer (geometric mean titer [GMT], 49) in all of the participants after the third dose of NIPH-produced NZ strain vaccine [19]. Preassigned targets from MeNZB immunogenicity trials in childhood were met or surpassed in all age groups (8–12 years, 16–24 months, 6–8 months, and 6–10 weeks) [17, 20–22]. However, a fourth dose was required in 6–10-week-old infants to reach antibody levels achieved after 3 doses in older children [22]. There was an age gradient in GMT, as was seen in previous OMV vaccine evaluations [16, 30, 37]. Titers were modest, compared with those measured after meningococcal C and A conjugate vaccinations (figure 4) [23, 58, 59], but were comparable to those found in other published meningococcal B OMV trials involving children [16]. Overall, MeNZB was given to ~1300 children, with no serious adverse events. Despite frequent mild to moderate injection site reactions, which lasted 2–3 days, tolerability was high, with excellent trial retention. Severe reactogenicity was uncommon, and there were some self-limited systemic reactions. Follow-up studies of antibody level decrease revealed rapid decreases in all age groups, especially the youngest (figure 3). Only 27.5% of infants aged 6–8 months who were tested 7 months after the 3-dose priming series had an serum bactericidal antibody titer ≥1:4. Therefore, most infants and children are likely to be unprotected not long after immunization (figure 4) [30, 31] if a titer of ≥1:4 is considered as a putative correlate of protection [31]. A vigorous booster response suggesting memory, although with modest GMTs, was seen both in children aged 16–24 months who had initially responded to 3 doses of vaccine (GMT, 259; 95% confidence interval [CI], 184–363) and in those who had not (GMT, 69; 95% CI, 46–106) [18].

**LICENSURE AND EPIDEMIC CONTROL**

Provisional licence was granted by the NZ licensing authority (Medsafe) for persons aged 6 months to 19 years in July 2004 and for persons aged ≥6 weeks in February 2005. In January 2006, the inclusion of a fourth dose in the infant priming series was recommended on the basis of additional trial data.

Vaccination commenced in July 2004, and by June 2006, >3
million doses had been administered to 1 million young persons aged <20 years as part of a catch-up program. Vaccine continued to be offered to infants with the routine schedule until 1 June 2008. In its final report, the ISMB stated that there was “an outstanding program of sensitive and objective safety monitoring” and that “it found no evidence of any significant adverse health event associated with the vaccine” (T. Nolan, C. Whitney, C. Grant, P. Reid, C. Frampton, unpublished data).

NZ’s epidemic of meningococcal disease, which began in 1991, began to wane in the last year of the trials and before the vaccine program commenced (figure 1). Earlier documented epidemics of serogroup B lasted 10–15 years and then naturally ended [6, 16, 60]. The extent of vaccine efficacy, especially in children aged <5 years, who carried 50% of the disease burden, remains uncertain [44, 52, 53, 56, 61].

On the basis of current available evidence on vaccine prevention of meningococcal disease, persistence of antibody is considered to be necessary to provide protection [62]. This has been best established for serogroup C, although it is unlikely to be different for serogroup B [16, 30, 36]. Laboratory studies [63] demonstrated an important delay (~5 days) before titer increase after administration of a booster to already primed infants. Meningococcal disease is known to ensue soon after the organism is acquired in the nasopharynx; thus, 5 days may not be fast enough to prevent invasive disease. The observation of waning immunity to meningococcal C disease in UK infants in a vaccinated population [64] lends support to the notion that sufficient circulating antibodies are necessary for protection. This led to a dose schedule change for UK infants for meningococcal C vaccine. MeNZB vaccination was not expected to provide long-term bactericidal antibody levels. Published literature shows a sharp decrease after receipt of 4 doses of vaccine, even in adults [40, 42].

In our studies (figure 3), among infants aged 6–8 months, only 27.5% had a serum bactericidal antibody titer ≥1:4 (i.e., had antibody likely to protect at 7 months after the third dose of vaccine) [18]; among preteens in cohort A, 35.5% (95% CI, 24.8%–48.0%) had a serum bactericidal antibody titer ≥1:4 at 14 months after the third dose (figure 3). Antibody level decrease after the fourth dose of the priming series in the youngest age group in immunogenicity trials (age, 6–10 weeks) was not studied, although only 27.5% had a serum bactericidal antibody titer ≥1:4 when blood samples were obtained 4.5 months after 3 doses of MeNZB; the fourth dose produced only a modest increase in GMT to 21.3 (95% CI, 12.3–36.7) (figure 3) [22].

Therefore, since the completion of the mass vaccination campaign in late 2005, most children have been unlikely to have any antibody protection against the NZ meningococcal epidemic strain as a result of the rapid decrease in antibody levels after vaccination. In addition, administration of the scheduled 4-dose priming series to infants was poor (50%–60% reported by the NZ Ministry of Health in 2008). Despite this, the epidemic continues to wane (in 2008, the rate of disease due to the epidemic strain was 1.1 cases per 100,000 population).

MeNZB vaccine ceased to be offered in NZ after 1 June 2008. Active disease surveillance remains in place. A robust booster response has been shown with MeNZB in children aged 16–24 months [18], and the booster, along with reinstatement of infant vaccination (vaccine is stock piled), could be used for epidemic control among high-risk age groups if there is a resurgence of disease. New serogroup B vaccines consisting of recombinant protein antigens with bactericidal activity that were chosen from the sequenced genome may give hope for the future control of endemic meningococcal disease [24, 65]. However, preliminary data (figure 4) suggest that such a vaccine combined with OMV from the NZ epidemic strain, after 3 and 4 doses in infants, produced similar low GMTs against the NZ strain in vitro, compared with our studies of MeNZB vaccine alone (3 or 4 doses). GMTs against 2 other serogroup B outer membrane proteins were more robust. Longer durations between administration of doses in this infant age group could have some benefit.

CONCLUSIONS

OMV vaccines are the only currently available tool for control of outbreaks dominated by serogroup B. The NZ experience suggests a role for OMV vaccines as a “circuit breaker” in an epidemic of strain-specific serogroup B meningococcal disease, with a more rapid than expected decrease in the number of cases in the first year after mass vaccination (C. Kelly, R. Arnold, Y. Galloway, J. O’Hallahan, unpublished data). Because serum bactericidal antibody titers (which indicate protection) decreased rapidly, it would be expected that there has been minimal vaccine effect for >2 years after the mass campaign. There has been no resurgence of disease, which allowed the safe discontinuation of MeNZB vaccine in June 2008. Careful ongoing surveillance will be essential. Vaccine intervention may have been more effective (and cost-effective) if it was started earlier during the epidemic cycle.

Acknowledgments

We thank all of those involved in the MeNZB vaccination program.

Financial support. New Zealand Ministry of Health and Chiron Vaccines (now Novartis Vaccines).

Potential conflicts of interest. M.H. has received funding from the Meningitis Foundation UK. D.L. has received travel funds from the New Zealand Ministry of Health, Novartis Vaccines, and Wyeth and serves on the Vaccine Advisory Board for GlaxoSmithKline Vaccines (the Asia/Pacific region). C.J. has accepted travel funds from Merck. S.R. has received travel funds from the New Zealand Ministry of Health, Novartis Vaccines, and Wyeth, Merck, and GlaxoSmithKline and serves on the Vaccine Advisory Board for GlaxoSmithKline Vaccines (the Asia/Pacific region). S.W. and J.S.: no conflicts.
References


32. Martin DR, Ruijne N, McCallum L, O’Hallahan J, Oster P. The VR2 epitope on the PorA P1.7–2.4 protein is the major target for the immune response elicited by the strain-specific group B meningococcal vaccine MenNZB. Clin Vaccine Immunol 2006; 13:486–91.


41. Fischer M, Carlone GM, Holst J, Williams D, Stephens DS, Perkins


