Updated antibiotic resistance and clinical spectrum of infections caused by *Streptococcus pneumoniae* in Taiwan: Emphasis on risk factors for penicillin nonsusceptibilities

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**KEYWORDS**
Antibiotic resistance; Penicillin nonsusceptibility;
Streptococcus pneumoniae

Introduction

Streptococcus pneumoniae is one of the most common pathogens causing community-acquired infections. The major invasive pneumococcal diseases include pneumonia, bacteremia, and meningitis and can result in high mortality despite antimicrobial therapy, ranging from 20% to 50%. Penicillin used to be the most important antibiotic against invasive pneumococcal diseases. However, resistance to penicillin has been noted since 1967. Prior to 2008, the penicillin susceptibility breakpoint for S. pneumoniae was 0.12 μg/mL. In 2008, Clinical and Laboratory Standards Institute (CLSI) provided two different criteria for penicillin susceptibility.

Methods: Isolates of S. pneumoniae collected from six hospitals participating in the Taiwan Surveillance of Antimicrobial Resistance (TSAR) program (2002, 2004, 2006, 2008) were enrolled in this study. Bacterial susceptibilities were determined by the minimum inhibitory concentration. The clinical data of source patients were collected retrospectively.

Results: A total of 330 nonduplicate S. pneumoniae isolates were enrolled in this study. Sputum was the most common specimen source, followed by pus. The mean age of the source patients was 38 years among these 330 patients, and 247 had various infections caused by S. pneumoniae. The overall in-hospital mortality rate was 6% and most (60%) of the mortality occurred in patients older than 65 years. The mortality rates among the patients age 65 years and older and those age 5 years and younger were 12.9% (9 of 70) and 2.4% (2 of 83), respectively. The rates of nonsusceptibility to penicillin by the meningitis criteria (PNSP-M) were 69.0% in 2002, 81.0% in 2004, 73.7% in 2006, and 74.5% in 2008. Resistance to erythromycin and trimethoprim/sulfamethoxazole remained high. Using multivariate analysis, patients with PNSP isolates were more likely to have a history of antibiotic exposure within the previous 15 days compared with patients with penicillin-susceptible (PSSP) isolates (nonmeningitis criteria: 29.70% vs. 18.34%, \( p = 0.0288 \); meningitis criteria: 25.30% vs. 9.88%, \( p = 0.006 \)). Shock at presentation was the risk factor for in-hospital mortality.

Conclusion: Our study demonstrated that the rates of penicillin nonsusceptibility among S. pneumoniae remained high in Taiwan during the study period. Previous antibiotic exposure was the only risk factor for subsequent acquisition of penicillin-nonsusceptible S. pneumoniae compared with penicillin-susceptible S. pneumoniae. Judicious antibiotic use is important to control the spread of drug nonsusceptible S. pneumoniae.

Patients and methods

Bacterial isolates

S. pneumoniae isolates were collected as part of the Taiwan Surveillance of Antimicrobial Resistance (TSAR) program from medical centers and regional hospitals throughout Taiwan. The participating hospitals are located in the four geographic regions (northern, central, southern, and eastern) of Taiwan. TSAR has been conducted biennially since 1998 and data from TSAR I (1998) and II (2000) have been reported. TSAR III — VI (2002, 2004, 2006, 2008) isolates were collected between July and September from the same 26 hospitals, except for 2006 when isolates were from 25 hospitals. To obtain relevant clinical data, only the bacterial isolates and their source patients whose associated information could be obtained were enrolled in the current study. The associated demographic, clinical, and laboratory data of source patients from whom the bacteria were isolated were collected to investigate the risk factors for acquiring PNSP-M or PNSP-NM and mortality among patients with pneumococcal infections.

Antimicrobial susceptibility test

Antimicrobial susceptibilities to various antimicrobial agents, including penicillin, chloramphenicol, ceftriaxone,
erythromycin, trimethoprim/sulfamethoxazole, levo-
fl oxacin, and tetracycline were determined by MIC using
the CLSI reference microbroth dilution method.15 For
penicillin and ceftriaxone, M and M criteria were used.7
PNSP-NM referred to isolates with penicillin MIC ³ 4 µg/
ml whereas PSSP-NM (penicillin-susceptible *S. pneumoniae*
nonmeningitis) referred to isolates with penicillin
MIC ² 2 µg/ml using the NM criteria. PNSP-M referred to
isolates with penicillin MIC ³ 0.12 µg/ml whereas PSSP-M
isolates had penicillin MIC ³ 0.06 µg/ml using the M
criteria. Isolates with ceftriaxone MIC ³ 2 µg/ml and
² 1 µg/ml were considered ceftriaxone nonsusceptible and
susceptible, respectively, by the NM criteria. By the M
criteria, ceftriaxone nonsusceptible and susceptible *S
pneumoniae* referred to those with ceftriaxone MIC ³ 1 µg/
ml and ² 0.5 µg/ml, respectively.7

Statistical analysis
Continuous variables were described as mean ± standard
deviation (SD) and compared using the Student t test, or
described as the median as well as range and compared
with the Wilcoxon rank-sum test if their distributions
were not normal. Categorical variables were compared with
a chi-square test or Fisher exact test if the expected values
were less than 10. Risk factors for penicillin non-
susceptibility and all-cause in-hospital mortality were
identified using logistic regression models. Statistical
analyses were performed using SAS 9.1.3 (SAS Institute,
Cary, NC, USA). All tests were two-tailed and p < 0.05 was
considered statistically significant.

Results
A total of 331 pneumococcal isolates collected between
2002 and 2008 (corresponding to TSAR III-VI) and their
source patients from six hospitals, including three medical
centers and three regional hospitals, were enrolled in the
current study initially. One patient was excluded due to
missing data. Information on patient demographics and
clinical data is presented in Table 1. The mean age of the
330 patients from whom the isolates were obtained was 38
years. The male to female ratio was 217:96 (the sex of 17
patients was unknown). Sputum was the most common
specimen source, followed by pus/wound. The most
common underlying disease was cardiovascular disease.
Based on clinical data, 247 of the 330 patients were
determined to be infected and 70 were colonized (Table 1).

By NM criteria, the overall penicillin nonsusceptible rate
among the 330 studied isolates was 30.4% (Table 2). During
the study period, there was a transient decrease in PNSP-
NM in TSAR V (2006) isolates compared with isolates of
TSAR III, IV, and VI (p = 0.031) (Fig. 1). The overall non-
susceptibility to ceftriaxone was 19.4% by the NM criteria.
Almost all (92%) of the study isolates were resistant to
erythromycin and 70% were nonsusceptible to trimetho-
prim/sulfamethoxazole. Levofloxacin showed good activity
(TSAR III: 100%; TSAR IV: 95.1%; TSAR V: 97.4%; TSAR VI:
96.6%) against the tested isolates (Table 2).

By M criteria, the overall penicillin nonsusceptibility was
75.7%. The proportion of PNSP-M was also lower in isolates
of TSAR V compared with isolates of TSAR III, IV, and VI, but
the difference was not statistically significant (p = 0.549).
Sixty-three percent of the 330 pneumococci isolates were
nonsusceptible to ceftriaxone by the M criteria (Table 2).

Patients with PNSP-NM or PNSP-M isolates were more
likely to have a history of antibiotic exposure within the
previous 15 days compared with patients with PSSP by
either NM or M criteria (NM: 29.70% vs. 18.34%, p = 0.0288;
M: 25.30% vs. 9.88%, p = 0.006). Using univariate and
multivariate analysis by logistic regression models, previous
antibiotic exposure was an independent risk factor for
acquiring PNSP-NM or PNSP-M isolates (PNSP-NM, odds ratio
[OR]: 2.848, 95% confidence interval [CI]: 1.374-5.901, 
p = 0.0049; PNSP-M, OR: 3.730, 95% CI: 1.644-8.459,
p = 0.002) (Table 3). No specific antibiotic used previously
could be identified to be associated with acquiring PNSP.

Among the 247 pneumococci-infected patients, the
mean age was 36 years and lower respiratory tract infection
was the most common foci (144 of 247). PNSP-NM accounted
for 32% (79 of 247) of all invasive pneumococcal infections
and the overall in-hospital mortality was 6% (15 of 247). Sixty percent of the mortality cases (9 of 15)
occurred in patients older than 65 years. The mortality
rates among the patients older than 65 years and those
younger than 5 years were 12.9% (9 of 70) and 2.4% (2 of
83), respectively. There was no difference in mortality
between PSSP-NM and PNSP-NM infected patients or
between PSSP-M and PNSP-M infected patients (PSSP-NM vs.
PNSP-NM: 5.88% vs. 8.00%, p = 0.5755; PSSP-M vs. PNSP-M:
6.55% vs. 6.45%, p = 1.000). There was also no difference
in mortality between patients with infection caused by
ceftriaxone susceptible and nonsusceptible strains either
by NM or M criteria (NM criteria: 5.91% vs. 9.09%,
p = 0.4960; M criteria: 7.77% vs. 5.73%, p = 0.5950). Shock
at presentation was the only risk factor for in-hospital
mortality for patients with infection caused by *S. pneumo-
niae* either by univariate or multivariate analysis (OR: 40.1,
95% CI: 7.5 - 213.4, p < 0.0001).

Discussion
The emergence and rapid dissemination of antibiotic-
rresistant pneumococcal strains has been noted since the
1990s, and was found to be associated with previous anti-
biotic consumption.16,17 Our study of pneumococcal
isolates from six hospitals showed that the rates of peni-
cillin nonsusceptibility in *S. pneumoniae* in Taiwan, either
by M or NM criteria, remained high in Taiwan. However,
there was a transient decrease in penicillin non-
susceptibility in TSAR V (2006), especially by NM criteria
(p = 0.031).

Transient decreased penicillin nonsusceptibility in
pneumococci was also noted in the SENTRY Antimicrobial
Surveillance Program,9 and in a surveillance system in
Spain (Spanish Reference Laboratory for Pneumococci,
SRLP).18 In the SENTRY program, it was found that the
rates of β-lactam nonsusceptibility in pneumococci
increased during 1998-2001 but later decreased during
2002-2003, and then increased again during 2004 and 2009.
In that surveillance, penicillin and ceftriaxone non-
susceptibility of pneumococci (by NM criteria) in 2008 was
13.5% and 8.7%, values that were lower than our study of 30.4% and 19.4%, respectively. In SRLP, the prevalence of PNSP-M decreased in the past decade, especially during 2005–2008. The decrease of penicillin nonsusceptibility rate in both programs was proposed to be associated with the introduction of pneumococcal vaccine, which resulted in clonal shifts from multidrug-resistant (MDR) clones to non-MDR clones not covered by the vaccine. Studies on resistance in different serotypes in Taiwan have also shown that serotypes in PCV-7 vaccine have higher rates of

Table 1 Comparison of demographics and clinical characteristics of 330 patients with carriage or infection by S. pneumoniae stratified by penicillin susceptibility

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Nonmeningitis criteria</th>
<th>Meningitis criteria</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSAR (yr), n (%)</td>
<td>PSSP-NM (N = 229)</td>
<td>PNSP-NM (N = 101)</td>
<td></td>
</tr>
<tr>
<td>III (2002)</td>
<td>41 (17.90)</td>
<td>18 (18.00)</td>
<td>0.0081</td>
</tr>
<tr>
<td>IV (2004)</td>
<td>63 (27.51)</td>
<td>41 (41.00)</td>
<td></td>
</tr>
<tr>
<td>V (2006)</td>
<td>64 (27.95)</td>
<td>12 (12.00)</td>
<td></td>
</tr>
<tr>
<td>VI (2008)</td>
<td>61 (26.64)</td>
<td>29 (29.00)</td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD (y)</td>
<td>38.27 ± 30.68</td>
<td>39.00 ± 32.59</td>
<td>0.2527</td>
</tr>
<tr>
<td>Male to female</td>
<td>152/67</td>
<td>65/29</td>
<td>0.9630</td>
</tr>
<tr>
<td>Isolated specimen site, n (%)</td>
<td>Blood</td>
<td>16 (6.98)</td>
<td>14 (13.86)</td>
</tr>
<tr>
<td></td>
<td>Sputum</td>
<td>123 (53.71)</td>
<td>56 (55.45)</td>
</tr>
<tr>
<td></td>
<td>Urine</td>
<td>1 (0.44)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td></td>
<td>Pus/wound</td>
<td>47 (20.52)</td>
<td>20 (19.80)</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>24 (10.48)</td>
<td>9 (8.91)</td>
</tr>
<tr>
<td></td>
<td>Throat swab</td>
<td>12 (5.24)</td>
<td>1 (0.99)</td>
</tr>
<tr>
<td></td>
<td>Nasal swab</td>
<td>3 (1.31)</td>
<td>1 (0.99)</td>
</tr>
<tr>
<td>Underlying condition, n (%)</td>
<td>DM</td>
<td>30 (13.10)</td>
<td>14 (13.86)</td>
</tr>
<tr>
<td></td>
<td>Renal dx</td>
<td>7 (3.06)</td>
<td>2 (1.98)</td>
</tr>
<tr>
<td></td>
<td>CAD</td>
<td>45 (19.65)</td>
<td>23 (22.77)</td>
</tr>
<tr>
<td></td>
<td>Gl dx</td>
<td>12 (5.24)</td>
<td>8 (7.92)</td>
</tr>
<tr>
<td></td>
<td>Cancer</td>
<td>15 (6.55)</td>
<td>8 (7.92)</td>
</tr>
<tr>
<td></td>
<td>Immunosuppression</td>
<td>5 (2.18)</td>
<td>6 (5.94)</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>1 (0.43)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>39 (17.03)</td>
<td>13 (12.87)</td>
</tr>
<tr>
<td></td>
<td>Respiratory dx</td>
<td>30 (13.10)</td>
<td>20 (19.80)</td>
</tr>
<tr>
<td></td>
<td>Neurologic dx</td>
<td>23 (10.04)</td>
<td>16 (15.84)</td>
</tr>
<tr>
<td></td>
<td>Hepatic dx</td>
<td>13 (5.65)</td>
<td>8 (7.92)</td>
</tr>
<tr>
<td></td>
<td>Autoimmune dx</td>
<td>3 (1.31)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td></td>
<td>Living in LTCF or RCW</td>
<td>14 (6.11)</td>
<td>12 (11.88)</td>
</tr>
<tr>
<td></td>
<td>Hospitalization within</td>
<td>90 (39.30)</td>
<td>50 (49.50)</td>
</tr>
<tr>
<td>recent 1 y, n (%)</td>
<td>Invasive therapy (H/D,</td>
<td>10 (4.37)</td>
<td>1 (1.00)</td>
</tr>
<tr>
<td></td>
<td>C/T) within recent 1 y, n (%)</td>
<td>0 (0.00)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antibiotic use within</td>
<td>42 (18.34)</td>
<td>30 (29.70)</td>
</tr>
<tr>
<td>prior 15 days, n (%)</td>
<td>Infection or colonization, n (%)</td>
<td>51 (22.27)</td>
<td>19 (18.81)</td>
</tr>
<tr>
<td></td>
<td>Colonization</td>
<td>168 (73.36)</td>
<td>79 (78.21)</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>15 (6.98)</td>
<td>6 (5.94)</td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
<td>15 (6.98)</td>
<td>6 (5.94)</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; C/T = chemotherapy; DM = diabetic mellitus; dx = disease; Gl = gastrointestinal; H/D = hemodialysis; LTCF = long-term care facility; M = meningitis; NM = nonmeningitis; RCW = respiratory care ward; PNSP-M = penicillin-nonsusceptible S. pneumoniae meningitis; PSSP-M = penicillin-nonsusceptible S. pneumoniae meningitis; PNSP-NM = penicillin-nonsusceptible S. pneumoniae nonmeningitis; PSSP-NM = penicillin-susceptible S. pneumoniae nonmeningitis; SD = standard deviation; TSAR = Taiwan Surveillance of Antimicrobial Resistance.
penicillin nonsusceptibility.\textsuperscript{20,21} Therefore, the transient decrease of penicillin nonsusceptibility in \textit{S. pneumoniae} isolates collected in TSAR V (2006) might be related to the introduction of PCV-7 in Taiwan in 2005.

Our study also found that the proportion of PNSP-M was also lower in isolates of TSAR V compared with those of TSAR III, IV, and IV, but the difference was not statistically significant ($p = 0.549$). Fig. 2 demonstrates the cumulative distribution of MICs to penicillin of tested isolates. For the proportion of isolates with penicillin MIC $\leq 1$ µg/mL, that of isolates from TSAR V was only slightly higher than those from TSAR III, IV, and VI. However, for the proportion of isolates with a penicillin MIC of 2 µg/mL, that of isolates from TSAR V was much higher than those from TSAR III, IV, and VI. This is why there was a statistically significant decrease in PNSP-NM in TSAR V, but only a slight decrease (without statistical significance) in PNSP-M.

Decreased antibiotic usage resulting from restriction of antibiotics among patients in Taiwan with acute upper respiratory tract infection without clinical evidence of bacterial infection since 2001 has been reported.\textsuperscript{22} However, we did not find any decrease in rates of non-susceptibility to erythromycin, tetracycline, and trimethoprim/sulfamethoxazole, three of the commonly used first-line antibiotics in Taiwan outpatients, in pneumococci in Taiwan. One reason for this is that pneumococci in Taiwan are mostly MDR.\textsuperscript{10,11,14} Thus, the use of one of the antimicrobial agents would select for the MDR strains. The rates of erythromycin (92%) and trimethoprim/sulfamethoxazole (70%) nonsusceptibility in pneumococci in Taiwan remained much higher than isolates from the United States where nonsusceptibility to these two agents was 37% and 33%, respectively.\textsuperscript{9} Therefore, treatment choices are more limited for pneumococcal infections in Taiwan. Although resistance of pneumococci to levofloxacin did not increase significantly and remained at less than 5% overall during the study period, a finding similar to those from other countries,\textsuperscript{9,18,23} judicious use of this class of antibiotics is warranted.

Our study found that previous antibiotic exposure within 15 days before isolation of pneumococci was the only independent factor associated with penicillin non-susceptibility using either N or NM criteria. Previous antibiotic exposure would facilitate the subsequent acquisition of drug-resistant bacteria due to selection pressure.\textsuperscript{24,25} It was therefore reasonable that we found previous antibiotic use to be associated with PNSP-M or PNSP-NM carriage/infection in the current study. Although previous studies from other countries have reported similar findings,\textsuperscript{24,26–28} this is the first report demonstrating the association of antibiotic use and penicillin-nonsusceptible pneumococci in Taiwan.

Compared with PSSP-M, infection caused by PNSP-M has been associated with higher mortality in some studies,\textsuperscript{1,29} but some studies found no association between penicillin-nonsusceptibility and poorer patient outcome.\textsuperscript{30,31} In the current study we found no significant difference in the mortality of patients infected by PSSP-M and PNSP-M or between PSSP-NM and PNSP-NM isolates but shock at presentation was significantly associated with in-hospital mortality in infected patients. The overall in-hospital mortality rate of pneumococcal disease in our study was 6%, a rate lower than those reported in previous studies, which ranged from 14% to 23%.\textsuperscript{31–33} The mortality rates among the patients age 65 years and older and age 5 years and younger (12.9% and 2.4%, respectively) were also lower than previous reports.\textsuperscript{34,35} Our study encompassed isolates from different sources and the proportion of patients with invasive pneumococcal disease was less than previous studies, which likely contributed to the lower mortality rate found in the current study. However, we did find 60% of

\begin{table}[h]
\centering
\caption{Antibiotic susceptibilities of \textit{S. pneumoniae} in different years\label{table:antibiotic-susceptibilities}}
\begin{tabular}{lcccccccc}
\hline
TSAR (y) & PEN-NM & PEN-M & CRO-NM & CRO-M & ERY & TMP/SMX & LVX & CHL & TCY \\
\hline
TSAR-III (2002) & 69.5 & 31.0 & 78.1 & 44.1 & 10.2 & 37.2 & 100 & 49.2 & 3.3 \\
TSAR-IV (2004) & 60.5 & 19.0 & 85.6 & 32.7 & 9.4 & 23 & 95.1 & 55.1 & 6.7 \\
TSAR-V (2006) & 84.2 & 26.3 & 90.7 & 43.4 & 10.5 & 26.3 & 97.4 & 60.6 & 5.3 \\
TSAR-VI (2008) & 67.7 & 25.5 & 78.9 & 32.2 & 5.6 & 33.3 & 96.6 & 41.7 & 4.4 \\
Overall & 69.6 & 24.3 & 80.6 & 37.1 & 7.9 & 29.2 & 97 & 55.7 & 5.2 \\
\hline
\end{tabular}
\begin{flushleft}
CHL = chloramphenicol; CRO-M = ceftriaxone by meningitis criteria (susceptible, minimum inhibitory concentration [MIC] $\leq 0.06$ ug/mL; nonsusceptible, MIC $> 0.06$ ug/mL); CRO-NM = ceftriaxone by nonmeningitis criteria (susceptible, MIC $\leq 1$ ug/mL; nonsusceptible, MIC $> 1$ ug/mL); ERY = erythromycin; LVX = levofloxacin; PEN-M = penicillin by meningitis criteria (susceptible, MIC $< 0.06$ ug/mL; nonsusceptible, MIC $\geq 0.06$ ug/mL); PEN-NM = penicillin by meningitis criteria (susceptible, MIC $< 1$ ug/mL; nonsusceptible, MIC $\geq 1$ ug/mL); TMP/SMX = trimethoprim/sulfamethoxazole; TSAR = Taiwan Surveillance of Antimicrobial Resistance.
\end{flushleft}
\end{table}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Trends of penicillin and ceftriaxone susceptibility in Taiwan Surveillance of Antimicrobial Resistance (TSAR) periods.\label{figure1}}
\end{figure}

### Table 3
Factors significantly associated with carriage or infection by PNSP-M or PNSP-NM; results by univariate analysis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Nonmeningitis criteria</th>
<th>Meningitis criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>TSAR III (2002)</td>
<td>1.404</td>
<td>0.718</td>
</tr>
<tr>
<td>TSAR IV (2004)</td>
<td>0.405</td>
<td>0.178</td>
</tr>
<tr>
<td>TSAR V (2006)</td>
<td>1.026</td>
<td>0.509</td>
</tr>
<tr>
<td>Antibiotic use within prior 15 days</td>
<td>1.852</td>
<td>1.062</td>
</tr>
</tbody>
</table>

TSAR = Taiwan Surveillance of Antimicrobial Resistance; PNSP-M = penicillin-nonsusceptible *S. pneumoniae* meningitis; PNSP-NM = penicillin-nonsusceptible *S. pneumoniae* nonmeningitis.

Figure 2. Cumulative distribution of minimum inhibitory concentrations (MICs) of *S. pneumoniae* to penicillin from Taiwan Surveillance of Antimicrobial Resistance (TSAR) III to TSAR VI.

the mortality cases in our study occurred in patients age 65 years and older, which is compatible to the previous finding that older age (≥ 65 years) is significantly associated with case-fatality of invasive pneumococcal disease.34

In conclusion, we found that penicillin nonsusceptibility of *S. pneumoniae* in Taiwan remained high, albeit a transient decrease was noted during the study period. Although we did not find significant difference in mortality in patients infected with penicillin-nonsusceptible and -susceptible isolates, we did show that previous antibiotic exposure was an independent factor associated with subsequent acquisition of penicillin-nonsusceptible pneumococci. Therefore, judicious antibiotic use is an important measure to control the spread of penicillin-nonsusceptible pneumococci. Continued surveillance is needed to monitor changes in pneumococcal resistance as vaccination programs change in Taiwan.

### References


