紐蒙肺®
多價性肺炎鏈球菌疫苗
PNEUMOVAX® 23
(PNEUMOCOCCAL VACCINE POLYVALENT)

V110-TWN-2014-008757
衛署菌疫輸字第 000492 號
本藥須由醫師處方使用

說明

(下述流行病學資料主要是大規模接種肺炎鏈球菌疫苗前之數據)

PNEUMOVAX® 23 （多價性肺炎鏈球菌疫苗）為一經由肌肉注射或皮下注射的滅菌液狀疫苗。本疫苗含有經高度純化 23 種最普遍或最具侵襲性的肺炎鏈球菌型(pneumococcal types of *Streptococcus pneumoniae*)的細菌莢膜多醣體 (capsular polysaccharides)之混合物；其中包括六種在美國兒童與成人間最常引發侵犯性和抗藥性肺炎鏈球菌感染的血清型（見表一）。依據在美國進行之調查，本疫苗所含之 23 種菌株莢膜至少涵蓋了 90%自肺炎病人血液中分離之菌種，及 85%應為無菌環境部位分離之菌種。

PNEUMOVAX 23 的製造方法是根據美國默克藥廠研發出的方法。每 0.5 mL 劑量中含有 23 種細菌莢膜多醣體，每種莢膜多醣體各 25 μg，溶於含有 0.25%酚作為保存劑之等張生理食鹽水中。

表一 PNEUMOVAX 23 內所含之 23 種肺炎鏈球菌莢膜型

命名	肺炎鏈球菌血清型
丹麥	1 2 3 4 5 6B** 7F 8 9N 9V** 10A 11A 12F 14** 15B 17F 18C 19F** 19A** 20 22F 23F** 33F

** 為最常造成抗藥性肺炎鏈球菌感染的血清型

臨床藥理學

肺炎鏈球菌感染是世界上的主要死因之一，而且是引起肺炎、菌血症、腦膜炎及中耳炎的主要因素。

在美國及世界其他地方，具有抗藥性的肺炎鏈球菌(*Streptococcus pneumoniae*)逐漸增加。在某些區域，曾報導高達 35%的肺炎鏈球菌分離菌株對 penicillin 產生抗藥性。許多對 penicillin 產生抗藥性的肺炎鏈球菌亦會對其他抗生素(如 erythromycin, trimethoprim-sulfamethoxazole 和廣效性的 cephalosporins)產生抗藥性；因此以注射疫苗來預防肺炎鏈球菌疾病愈顯得重要。

流行病學

每年在美國因肺炎鏈球菌感染約造成 40,000 人死亡。美國每年至少發生 500,000 例的肺炎鏈球菌肺炎。因罹患細菌性肺炎而需住院的病人中，肺炎鏈球菌約佔 25-35%的病因。

每年在美國因肺炎鏈球菌疾病而造成約 50,000 例的肺炎鏈球菌性菌血症。一些研究顯示每年整體的菌血症發生率為每 100,000 人有 15-30 例；65 歲以上的年齡層發生率則為每 100,000 人有 50-83 例，而兩歲以下的幼童則為每 100,000 人有 160 例。

後天免疫不全症候群(AIDS)患者之肺炎鏈球菌性菌血症發生率高達 1%（每 100,000 人有 940 例）。

在美國，白人罹患菌血症的機率較一些其他人種（如黑人、阿拉斯加原住民、美洲印地安人）低。

即使採取適當的抗生素療法及密切的醫療照顧，成人因罹患肺炎鏈球菌性菌血症所造成的死亡率為 15-20%，而老年人則為 30-40%。居住在城市內的成人因罹患肺炎鏈球菌性菌血症的平均死亡率為 36%。

在美國每年肺炎鏈球菌疾病約造成 3000 例的腦膜炎。每年整體的肺炎鏈球菌性腦膜炎發生率為每 100,000 人有 1-2 例。六至二十四個月大的嬰幼兒及六十五歲以上(含 65 歲)的老年人罹患肺炎鏈球菌性腦膜炎的機率最高；黑人的罹患率為白種人和西班牙人的兩倍。復發性肺炎鏈球菌腦膜炎會發生在因先天性損傷、頭顱破裂或進行神經手術造成慢性腦脊髓液外溢的病人身上。

即使使用抗生素來有效的控制細菌，侵犯性的肺炎鏈球菌性疾病（如菌血症或腦膜炎）和肺炎仍會引起高的罹病率及死亡率。這些肺炎鏈球菌性疾病所造成的影響，主要是因為在發病後的前五天，入侵的細菌會引發不可回復的生理性傷害而導致。接種疫苗提供了降低此種疾病罹病率及死亡率之一有效方法。

危險因素

非常年輕和六十五歲以上(含 65 歲)的年齡層以及慢性疾病的患者，都易罹患肺炎鏈球菌感染及嚴重的肺炎鏈球菌性疾病。

患有慢性心血管疾病（如充血性心衰竭或心肌症）、慢性肺臟疾病（如慢性阻塞性肺疾病或肺氣腫）或慢性肝病（如肝硬化）、糖尿病、酒精中毒或氣喘（同時伴有慢性支氣管炎、肺氣腫或長期使用全身性類固醇）的病人罹患肺炎鏈球菌性疾病的危險性會增高。成年人一般而言具有免疫力。

因免疫抑制（先天性免疫缺乏、人類免疫缺乏病毒[HIV]感染、白血病、淋巴瘤、多發性骨髓瘤、Hodgkin 氏症或全身性惡性腫瘤）；器官或骨髓移植；使用烷化基劑、抗代謝藥物或全身性類固醇；慢性腎衰竭或腎病症候群，而對多醣體抗原反應降低或血清抗體濃度降低的病人屬於高危險群。

功能或解剖上無脾臟者（鐮狀細胞性貧血或脾臟切除）是感染肺炎鏈球菌的最高危險群，因為在此情況下，會導致血管中莢膜化細菌的清除功能降低。患有鐮狀細胞性貧血或脾臟切除的兒童會增加罹患猛暴型肺炎鏈球菌性敗血症的機率，這疾病常伴隨高死亡率。

免疫性

已經證實純化的肺炎鏈球菌莢膜多醣體，能誘導人體產生抗體，此種抗體能有效預防肺炎鏈球菌疾病。在人體試驗中注射多價性疫苗後，已證實 23 種莢膜中的任一種均能引導出免疫力。

以含 12 種、14 種和 23 種莢膜之肺炎鏈球菌疫苗對兩歲以上(含兩歲)孩童或各年齡層之成人所進行之研究，顯示均能產生免疫反應。通常於接種後的第三週，即可達到具有保護力的專一性莢膜抗體濃度。

細菌莢膜多醣體誘導出產生的抗體，主要是經由與 T 細胞無關(T-cell-independent)的機轉。兩歲以下的嬰兒由於免疫系統尚未完全發展，因此對大部分肺炎鏈球菌莢膜所產生的抗體反應能力通常較差或不一致。

有效性

研究含 6 種或 12 種多醣體莢膜之肺炎鏈球菌疫苗保護效果的兩個臨床對照試驗已在南非對年輕、健康的金礦礦工進行，這些礦工們都是罹患肺炎鏈球菌性肺炎和菌血症的高危險群。從觀察其注射疫苗後二週至一年發生肺炎鏈球菌性肺炎的機率結果顯示，這兩種疫苗的保護力為含 6 種莢膜有 76%保護效果，而含 12 種莢膜疫苗有 92%的保護效果。

另外由 Dr. R. Austrian 和其同事使用類似的肺炎鏈球菌疫苗在美國「國家過敏性及感染性疾病中心」所做的研究顯示，能降低疫苗內所含莢膜型引起之肺炎達 79%，而降低專一型態之肺炎鏈球菌性菌血症達 82%。在法國所進行的臨床試驗顯示，肺炎鏈球菌疫苗能有效降低看護中心內人員罹患肺炎的機率達 77%。

在美國所進行的兩個上市後隨機分配的對照性試驗顯示，老年人或具有慢性疾病的病人在接種多種莢膜多醣體疫苗後並不能支持此疫苗對非菌血性肺炎的有效性。然而，這些試驗缺乏足夠的統計能力去分析接種疫苗組和無接種疫苗組間非細菌性肺炎發生率之差異。

針對一個含有九個隨機分佈，對照性的臨床試驗進行 meta-analysis 後，顯示肺炎鏈球菌疫苗能有效減少低危險群（但非高危險群）之成人罹患非菌血性肺炎鏈球菌肺炎的發生率。因為缺乏專一且具敏感性的非菌血

性肺炎鏈球菌性肺炎之診斷方法。這些研究的參考價值可能受限，莢膜多醣體之肺炎鏈球菌疫苗不能有效的預防兒童上呼吸道疾病。
最近多次對照控制臨床研究顯示，肺炎鏈球菌疫苗可有效地預防嚴重的肺炎鏈球菌疾病。在有免疫力接種者之點估計(point estimates)為 56%到81%。
僅有一個對照性研究顯示對菌血症並無效果，這可能是受試者數目少及接種疫苗的情形不完整所致。此外試驗組和對照組間潛在的健康狀況並不相當，因此造成偏差，而低估了疫苗的有效性。
根據「疾病防治中心」肺炎鏈球菌監視系統所進行的血清型態流行程度的研究顯示疫苗對與疫苗內所含相同血清型態之細菌所引起的侵犯性感染所達成的保護效果，對六歲以上(含六歲)者，可以提供 57%的保護效果，對特別的患者群（如糖尿病、冠狀動脈疾病、充血性心衰竭、慢性肺疾病和無脾臟患者）則有 65-84%的保護效果，而對六十五歲(含六十五歲)以上具免疫力者則有 75%的保護效果。疫苗在某些免疫不全患者的效果未被確認；而且進行試驗時，亦無法從每一疾病的族群中招募足夠未接種疫苗的病人。
在較早期的研究顯示，患有鐮狀細胞性疾病、先天性無脾臟或進行脾臟切除手術之二至二十五歲的兒童及青年在接種疫苗後顯然比未接種疫苗者更少發生細菌性肺炎鏈球菌性疾病。

免疫力持續的時間

接種肺炎鏈球菌疫苗後，經過五至十年後，對血清型專一性的抗體濃度會下降。在某些群體（如兒童）抗體濃度下降的速度會更快。有限的資料顯示在六十歲以上的老年人，抗體濃度可能下降。
美國預防接種諮詢委員會(The Advisory Committee on Immunization Practices; ACIP) 表示這些現象顯示須追加接種疫苗以提供持續保護的效果。（見使用方法中，追加接種一欄）
一項流行病學的研究結果顯示，在第一次接種疫苗後至少可提供九年的保護。曾有報告顯示在接種疫苗後，疫苗的效果會隨時間的增長而降低，此現象尤其在特別年長者（八十五歲及八十五歲以上者）更明顯。

適應症

預防肺炎鏈球菌性肺炎及肺炎鏈球菌性菌血症

說明：PNEUMOVAX 23 其適應症是用來增加對因由本疫苗所含之肺炎鏈球菌型所引起之肺炎鏈球菌疾病的人體免疫力。本疫苗其預防肺炎鏈球菌性肺炎及肺炎鏈球菌性菌血症的效果已在有對照組的臨床試驗中得到證實。
PNEUMOVAX 23 疫苗對於不屬於本品內所含莢膜型之肺炎鏈球菌引起之肺病，無預防效果。

使用方法

PNEUMOVAX 23 建議使用在下列的人：

- 五十歲或五十歲以上定期接種 *
- 兩歲及兩歲以上患有特定慢性疾病或居住在特別環境或社會環境者

美國 ACIP 對於肺炎鏈球菌疾病的預防有疫苗特定的建議。可參考：http://www.cdc.gov/mmwr/PDF/rr/rr4608.pdf 及 http://www.cdc.gov/vaccines/recs/provisional/downloads/pneumo-Oct-2008-508.pdf
* 註：美國 ACIP 建議 65 歲及 65 歲以上成人定期接種

接種疫苗時間

如果可能，至少在接受脾臟切除手術前兩週接種肺炎鏈球菌疫苗。
對於計劃進行癌症化學療法或其他免疫抑制療法者（如患有 Hodgkin 氏症或進行器官或骨髓移植者），施打肺炎鏈球菌疫苗之後應間隔至少二週以後再開始免疫抑制療法。避免在接受化學療法或放射性療法期間接種疫苗。依據文獻報導，宜及早於在完成腫瘤疾病的化學療法或放射性療法後的幾個月內接種肺炎鏈球菌疫苗。對 Hodgkin 氏症者，在接受密集的化學療法（同時有或無放射性療法）之後兩年甚或更久，對疫苗接種的免疫反應會受影響而打折扣。對一些接受治療後與接種肺炎鏈球菌疫苗的時間間隔較久的病人，在完成化學療法或免疫抑制療法之後的兩年期間，有較佳的抗體反應。
對於無症狀或有症狀之 HIV 感染者，在 HIV 感染診斷確定後，應儘快接種疫苗。

併用其他疫苗

美國 ACIP 表示同時接種肺炎鏈球菌疫苗和流行性感冒疫苗時(分別注射在不同手臂），不會增加副作用或減少對任一種疫苗的抗體反應。與肺炎鏈球菌疫苗不同，對特別的族群建議每年均接種流行性感冒疫苗。

追加接種

ACIP 建議先前曾接種 PNEUMOVAX 23 或肺炎鏈球菌接合疫苗之高危險群者再追加接種疫苗。
當 PNEUMOVAX 23 用於追加接種時，在皮下或肌肉注射 0.5mL 單一劑量。

禁忌

不可用於對本疫苗內任何成份過敏者。若對疫苗內的任何成份發生急性過敏反應時必須馬上注射 Epinephrine（濃度 1：1000）。

警告

對於計劃進行癌症化學治療或免疫抑制療法（如 Hodgkin 氏症或進行器官或骨髓移植者），接種疫苗的時間很重要。（見使用方法中，接種疫苗時間一欄）
如果疫苗使用於正在接受免疫抑制療法的病人，可能無法獲得預期的抗體反應，而且會嚴重破壞未來對肺炎鏈球菌抗原的免疫反應。（見使用方法中，接種疫苗時間一欄）
皮內(intradermal)注射可能造成嚴重的局部反應。

注意事項

一般人

對於患有嚴重心血管及/或肺功能損傷，其全身性反應可能導致明顯危險的病人，須在注射 PNEUMOVAX 23 後給予注意及適當的照顧。
患有任何發熱性呼吸道疾病或其他活動性感染症(active infection)者必須暫緩注射 PNEUMOVAX 23，除非醫師認為暫停注射本疫苗會有更高的危險時才能使用本品。
對於需要以 penicillin（或其他抗生素）來預防肺炎鏈球菌感染的病患，在注射 PNEUMOVAX 23 後，不應停止使用此預防性的抗生素。
PNEUMOVAX 23 可能對因先天性損傷、頭顱破裂或進行神經手術造成慢性腦脊髓液外溢的病人沒有預防的效果。
對於先前曾接種 23 種細菌莢膜多醣體疫苗的免疫功能正常者，並不建議定期追加接種疫苗。然而對於年齡≧ 2 歲且易患嚴重肺炎鏈球菌感染的高危險群者及肺炎鏈球菌抗體濃度快速下降者，建議再追加接種一次疫苗。（見使用方法中，追加接種）

醫護人員須知

醫護人員應了解病人目前的健康狀況和先前接種疫苗的情形。（見使用方法中，追加接種）
醫護人員應詢問病人，其雙親或看護者有關先前接種 PNEUMOVAX 23 或其他肺炎鏈球菌疫苗的反應。

病患須知

醫護人員應提供病人、其雙親或看護者有關接種疫苗的益處及危險性。與疫苗相關的危險性請參見警告、注意事項和不良反應。應告知病患、其雙親或看護者 PNEUMOVAX 23 可能無法完全預防肺炎鏈球菌的感染。
病人、家長以及看護者也應被告知，如果接種後發生任何嚴重的不良反應時，必須通知醫護人員，醫護人員也應該將狀況反應給製造廠商。

懷孕婦女

懷孕危險等級 C：尚無以 PNEUMOVAX 23 進行之動物生殖試驗。目前亦不知懷孕婦女注射 PNEUMOVAX 23 後是否會造成胎兒的傷害或影響其生育力。只有在明確知道必要施打本疫苗的情況下，孕婦才能注射本

疫苗。

授乳婦女

目前尚不知本品是否會分泌至人類乳汁。因為許多藥品均會分泌入人類的乳汁中，因此注射 PNEUMOVAX 23 的授乳婦女須注意。

小兒使用

PNEUMOVAX 23 並不建議使用在小於兩歲的兒童。小於兩歲的嬰幼兒其對 PNEUMOVAX 23 的安全性及有效性尚未建立。此年齡層的兒童對肺炎鏈球菌疫苗所含的莢膜多醣體反應不佳。(見臨床藥理學中，免疫性一欄)

老年人使用

有多項上市前後執行的 PNEUMOVAX 23 臨床試驗收錄 65 歲或更年長之受試者，其中一項最大型的試驗中，比較 65 歲或更年長之受試者(n=629)與 50 至 64 歲的受試者(n=379)接種 PNEUMOVAX 23 的安全性。此試驗收錄非臥床的受試者且其年齡相關之慢性疾病之盛行率與一般人相似(可預期)。臨床資料並沒有顯示 65 歲或更年長之受試者的不良反應發生率或嚴重度較 50 至 64 歲之受試者增加。但畢竟高齡者身體狀況可能不似年輕般可耐受醫療處置，所以不能排除年長者有較高發生不良反應的頻率及/或較嚴重的反應的可能。上市後研究報告中，一些虛弱且具多重合併疾病的年長者在疫苗接種後有嚴重不良經驗與複雜性臨床發展。

不良反應

在臨床試驗中 PNEUMOVAX 23 最常見的不良經驗報告是：
注射部位的局部反應包括酸痛、紅斑、溫熱感及結塊。
高燒≦ 38.9°C (102°F)。

其他在臨床試驗及上市後的使用經驗中 PNEUMOVAX 23 曾報告的其他不良經驗包括：
全身性的異常及投藥部位狀態：蜂窩性組織炎、衰弱、身體不適、發燒〔＞38.9°C (102°F)〕、發冷、疼痛、四肢活動力降低、注射部位的肢體周圍腫脹。
消化系統：噁心、嘔吐。
血液/ 淋巴系統：淋巴腺炎、淋巴腺病變、血小板減少症（發生於患有病情穩定之自發性血小板減少性紫斑症之病人）、溶血性貧血（發生於患有其他血液疾病的病人）、白血球增生。
過敏反應包括：無防禦性過敏反應、血清病、血管神經性水腫。
肌肉骨骼系統：關節痛、關節炎、肌痛。
神經系統：頭痛、感覺異常、神經根部病變、Guillain-Barre 氏症、熱痙攣。
皮膚：皮疹、蕁痲疹、多型性紅斑。
調查研究：血清 C 反應蛋白升高。

上市後的經驗顯示，注射部位的類蜂窩組織炎反應的報告很少見，在 1989 至 2002 年間之銷售量將近 4 千 3 百萬劑，這段期間的年報告率係每 100,000 劑小於或等於 2 個案例。無論是初次或重複接種，類蜂窩性組織炎發作時間中位數皆在疫苗接種後的 2 天內。
全身性症候與症狀，包括發燒、白血球增生以及血清 C 反應蛋白的檢驗值升高，可能與局部反應有關。
一項在臨床試驗中，於初次接種之後 3-5 年內追加接種本疫苗，觀察到局部反應的比率增加。
年齡大於或等於 65 歲之疫苗接種者所經歷之整體注射部位不良反應經驗在追加接種者的比率較初次接種者為高(分別為 79.3%及 52.9%)。年齡為 50 至 64 歲的疫苗接種者中，追加接種者與初次接種者所經歷之所有注射部位的不良經驗比率是相似的(分別為 79.6% 及 72.8%)。
在這兩個年齡層中，追加接種者所報告的綜合試驗終點(composite endpoint)比率高於初次接種者(綜合試驗終點係指下列任一者：注射部位的中度疼痛、嚴重疼痛及/或大型結節)。大於或等於 65 歲的疫苗接種者中，追加接種者與初次接種者所報告的綜合試驗終點比率分別是 30.6%及 10.4 %，而年齡為 50-64 歲之疫苗接種者中，追加接種者與初次接種者所報告的綜合試驗終點的比率分別為 35.5%及 18.9%。注射部位的反應發生於 3 天的監測或觀察期內且通常是在第 5 天前解除。
各年齡層初次接種者與追加接種者所經歷之所有全身性不良經驗的比率是相似的。就疫苗相關之全身性不良經驗比率而言，年齡≧ 65 歲追加接種者高於初次接種者(分別為 33.1 及 21.7%)，年齡 50~64 歲的接種者中之追加接種者則與初次接種者相似(分別為 37.5%及 35.5%)。
PNEUMOVAX 23 最常見的全身性不良經驗如下：衰弱/疲倦、肌痛及頭痛。無論年齡大小，於接受本疫苗後使用鎮痛劑所觀察到的增加比率(追加接種及初次接種分別是≦ 13%及≦ 4%)，皆於第 5 天前回復到基礎值。

劑量及使用方法

本疫苗不可靜脈或皮內注射(intradermal)。
所有的注射劑均需在使用前以眼睛檢視其溶液及瓶內是否含有異物或變色。PNEUMOVAX 23 為一澄清、無色之液體。本疫苗可直接使用不需稀釋或混合。本疫苗含有 0.25% Phenol 作為保存劑。
每位病人必須使用其個別的滅菌針頭及針筒以防止病人之間發生感染性疾病的傳染。
必須使用滅菌後的針頭及不含保存劑、抗菌劑及清潔劑的針筒從藥瓶內抽取 0.5 mL。
PNEUMOVAX 23 須於皮下(subcutaneous)或肌肉(intramuscular)注射（最好於上臂三角肌或大腿中段外側部位）0.5 mL，且須加以注意避免靜脈注射。
未開的藥瓶或已開的藥瓶均須存放在 2-8°C (36-46°F)。過期後必須丟棄，不可再用。

併用其他疫苗

美國 ACIP 表示同時接種肺炎鏈球菌疫苗和流行性感冒疫苗(分別注射在不同手臂），不會增加副作用或減少對任一種疫苗的抗體反應。與肺炎鏈球菌疫苗不同，對於適當的族群，建議每年均接種流行性感冒疫苗。

包裝

單一劑量小瓶，10 瓶盒裝
五劑量小瓶，10 瓶盒裝

製造廠：Merck Sharp & Dohme Corp.
廠　址：770 Sumneytown Pike, West Point, PA 19486, U.S.A.
包裝廠：Merck Sharp & Dohme B.V.
廠　址：Waarderweg 39, 2031 BN Haarlem, The Netherlands
藥　商：美商默沙東藥廠股份有限公司台灣分公司
地　址：台北市信義路五段 106 號 12 樓

PNEUMOVAX® 23

(PNEUMOCOCCAL VACCINE POLYVALENT)

DESCRIPTION (Epidemiology section below presents the data mainly before large scale vaccination)

PNEUMOVAX 23 (Pneumococcal Vaccine, Polyvalent), is a sterile, liquid vaccine for intramuscular or subcutaneous injection. It consists of a mixture of highly purified capsular polysaccharides from the 23 most prevalent or invasive pneumococcal types of *Streptococcus pneumoniae*, including the six serotypes that most frequently cause invasive drug-resistant pneumococcal infections among children and adults in the United States[1] (see Table 1). The 23-valent vaccine accounts for at least 90% of pneumococcal blood isolates and at least 85% of all pneumococcal isolates from sites which are generally sterile as determined by ongoing surveillance of U.S. data.[2]

PNEUMOVAX 23 is manufactured according to methods developed by the MERCK RESEARCH LABORATORIES. Each 0.5 mL dose of vaccine contains 25 μg of each polysaccharide type dissolved in isotonic saline solution containing 0.25% phenol as a preservative.

Table 1

23 Pneumococcal Capsular Types Included in PNEUMOVAX 23

Nomenclature	Pneumococcal serotypes
Danish	1 2 3 4 5 6B** 7F 8 9N 9V** 10A 11A 12F 14** 15B 17F 18C 19F** 19A** 20 22F 23F** 33F
**These serotypes most frequently cause drug-resistant pneumococcal infections [1]	

CLINICAL PHARMACOLOGY

Pneumococcal infection is a leading cause of death throughout the world[3] and a major cause of pneumonia, bacteremia, meningitis, and otitis media.

Strains of drug-resistant *S. pneumoniae* have become increasingly common in the United States and in other parts of the world. In some areas as many as 35% of pneumococcal isolates have been reported to be resistant to penicillin. Many penicillin-resistant pneumococci are also resistant to other antimicrobial drugs (e.g., erythromycin, trimethoprim-sulfamethoxazole and extended-spectrum cephalosporins), therefore emphasizing the importance of vaccine prophylaxis against pneumococcal disease.

Epidemiology

Pneumococcal infection causes approximately 40,000 deaths annually in the United States.[1] At least 500,000 cases of pneumococcal pneumonia are estimated to occur annually in the United States; *S. pneumoniae* accounts for approximately 25-35% of cases of community-acquired bacterial pneumonia in persons who require hospitalization.[1]

Pneumococcal disease accounts for an estimated 50,000 cases of pneumococcal bacteremia annually in the United States. Some studies suggest the overall annual incidence of bacteremia to be approximately 15 to 30 cases/100,000 population with 50 to 83 cases/100,000 for persons 65 years of age and older and 160 cases/100,000 for children less than two years of age.

The incidence of pneumococcal bacteremia is as high as 1% (940 cases/100,000 population) among persons with acquired immunodeficiency syndrome (AIDS).

In the United States, the risk of acquiring bacteremia is lower among whites than among persons in some other racial/ethnic groups (i.e., Blacks, Alaskan Natives, and American Indians).

Despite appropriate antimicrobial therapy and intensive medical care, the overall case-fatality rate for pneumococcal bacteremia is 15-20% among adults[4], and among elderly patients this rate is approximately 30-40%. An overall case-fatality rate of 36% was documented for adult inner-city residents who were hospitalized for pneumococcal bacteremia[1].

In the United States, pneumococcal disease accounts for an estimated 3,000 cases of meningitis annually. The estimated overall annual incidence of pneumococcal meningitis is approximately 1 to 2 cases per 100,000 population.The incidence of pneumococcal meningitis is highest among children six to 24 months and persons aged ≥ 65 years; rates for blacks are twice as high as those for whites or Hispanics. Recurrent pneumococcal meningitis may occur in patients who have chronic cerebrospinal fluid leakage resulting from congenital lesions, skull fractures, or neurosurgical procedures. [1]

Invasive pneumococcal disease (e.g., bacteremia or meningitis) and pneumonia cause high morbidity and mortality in spite of effective antimicrobial control by antibiotics.[4] These effects of pneumococcal disease appear due to irreversible physiologic damage caused by the bacteria during the first 5 days following onset of illness, [5,6] and occur regardless of antimicrobial therapy.[5,7] Vaccination offers an effective means of further reducing the mortality and morbidity of this disease.

Risk Factors

In addition to the very young and persons 65 years of age or older, patients with certain chronic conditions are at increased risk of developing pneumococcal infection and severe pneumococcal illness.

Patients with chronic cardiovascular diseases (e.g., congestive heart failure or cardiomyopathy), chronic pulmonary diseases (e.g., chronic obstructive pulmonary disease or emphysema), or chronic liver diseases (e.g., cirrhosis), diabetes mellitus, alcoholism or asthma (when it occurs with chronic bronchitis, emphysema, or long-term use of systemic corticosteroids) have an increased risk of pneumococcal disease. In adults, this population is generally immunocompetent.[1]

Patients at high risk are those who have a decreased responsiveness to polysaccharide antigen or an increased rate of decline in serum antibody concentrations as a result of: immunosuppressive conditions (congenital immunodeficiency, human immunodeficiency virus [HIV] infection, leukemia, lymphoma, multiple myeloma, Hodgkin's disease, or generalized malignancy); organ or bone marrow transplantation; therapy with alkylating agents, antimetabolites, or systemic corticosteroids; chronic renal failure or nephrotic syndrome.[1,8]

Patients at the highest risk of pneumococcal infection are those with functional or anatomic asplenia (e.g., sickle cell disease[9] or splenectomy), because this condition leads to reduced clearance of encapsulated bacteria from the bloodstream. Children who have sickle cell disease or have had a splenectomy are at increased risk for fulminant pneumococcal sepsis associated with high mortality.[1]

Immunogenicity

It has been established that the purified pneumococcal capsular polysaccharides induce antibody production and that such antibody is effective in preventing pneumococcal disease.[6,10] Clinical studies have demonstrated the immunogenicity of each of the 23 capsular types when tested in polyvalent vaccines. Studies with 12-, 14-, and 23-valent pneumococcal vaccines in children two years of age and older and in adults of all ages showed immunogenic responses.[10,11-14] Protective capsular type-specific antibody levels generally develop by the third week following vaccination.[13]

Bacterial capsular polysaccharides induce antibodies primarily by T-cell-independent mechanisms. Therefore, antibody response to most pneumococcal capsular types is generally poor or inconsistent in children aged < 2 years whose immune systems are immature. [1]

Efficacy

The protective efficacy of pneumococcal vaccines containing 6 or 12 capsular polysaccharides was investigated in two controlled studies of young, healthy gold miners in South Africa, in whom there was a high attack rate for pneumococcal pneumonia and bacteremia.[13] Capsular type-specific attack rates for pneumococcal pneumonia were observed for the period from 2 weeks through about 1 year after vaccination. Protective efficacy was 76% and 92%, respectively, in the two studies for the capsular types represented.

In similar studies carried out by Dr. R. Austrian and associates,[15] using similar pneumococcal vaccines prepared for the National Institute of Allergy and Infectious Diseases, the reduction in pneumonia caused by the capsular types contained in the vaccines was 79%. Reduction in type-specific pneumococcal bacteremia was 82%.

A prospective study in France found pneumococcal vaccine to be 77% effective in reducing the incidence of pneumonia among nursing home residents.[16]

In the United States, two postlicensure randomized controlled trials, in the elderly or patients with chronic medical conditions who received a multivalent polysaccharide vaccine, did not support the efficacy of the vaccine for nonbacteremic pneumonia.[17,18] However, these studies may have lacked sufficient statistical power to detect a difference in the incidence of laboratory-confirmed, nonbacteremic pneumococcal pneumonia between the vaccinated and nonvaccinated study groups.[1,19]

A meta-analysis of nine randomized controlled trials of pneumococcal vaccine concluded that pneumococcal vaccine is efficacious in reducing the frequency of nonbacteremic pneumococcal pneumonia among adults in low-risk groups but not in high-risk groups.[20] These studies may have been limited because of the lack of specific and sensitive diagnostic tests for nonbacteremic pneumococcal pneumonia. The pneumococcal polysaccharide vaccine is not effective for the prevention of common upper respiratory disease in children.

More recently, multiple case-control studies have shown pneumococcal vaccine is effective in the prevention of serious pneumococcal disease, with point estimates of efficacy ranging from 56% to 81% in immunocompetent persons.[1,21-26]

Only one case-control study did not document effectiveness against bacteremic disease possibly due to study limitations, including small sample size and incomplete ascertainment of vaccination status in patients.[27] In addition, case-patients and persons who served as controls may not have been comparable regarding the severity of their underlying medical conditions, potentially creating a biased underestimate of vaccine effectiveness.[1,19]

A serotype prevalence study, based on the Centers for Disease Control pneumococcal surveillance system, demonstrated 57% overall protective effectiveness against invasive infections caused by serotypes included in the vaccine in persons ≥ 6 years of age, 65-84% effectiveness among specific patient groups (e.g., persons with diabetes mellitus, coronary vascular disease, congestive heart failure, chronic pulmonary disease, and anatomic asplenia) and 75% effectiveness in immunocompetent persons aged ≥ 65 years of age. Vaccine effectiveness could not be confirmed for certain groups of immunocompromised patients; however, the study could not recruit sufficient numbers of unvaccinated patients from each disease group.

In an earlier study, vaccinated children and young adults aged 2 to 25 years who had sickle cell disease, congenital asplenia, or undergone a splenectomy experienced significantly less bacteremic pneumococcal disease than patients who were not vaccinated.[1,28]

Duration of Immunity

Following pneumococcal vaccination, serotype-specific antibody levels decline after 5-10 years.[1] A more rapid decline in antibody levels may occur in some groups (e.g., children)[1]. Limited published data suggest that antibody levels may decline in the elderly > 60 years of age. [29-30]

The Advisory Committee on immunization Practices (ACIP) states that these findings indicate that revaccination may be needed to provide continued protection.[1] (See INDICATIONS AND USAGE, Revaccination.)
The results from one epidemiologic study suggest that vaccination may provide protection for at least nine years after receipt of the initial dose.[22] Decreasing estimates of effectiveness with increasing interval since vaccination, particularly among the very elderly (persons aged ≥ 85 years) have been reported.[23]

INDICATIONS AND USAGE

PNEUMOVAX 23 is indicated for vaccination against pneumococcal disease caused by those pneumococcal types included in the vaccine. Effectiveness of the vaccine in the prevention of pneumococcal pneumonia and pneumococcal bacteremia has been demonstrated in controlled trials in South Africa, France and in case-control studies.
PNEUMOVAX 23 will not prevent disease caused by capsular types of pneumococcus other than those contained in the vaccine.

Vaccination with PNEUMOVAX 23 is recommended for selected individuals as follows:
- routine vaccination for persons 50 years of age or older†
- persons aged ≥ 2 years with *certain chronic conditions or* in special environments or social settings.[1,31]

The ACIP has vaccine specific recommendations for the prevention of pneumococcal disease.
Available from: http://www.cdc.gov/mmwr/PDF/rr/rr4608.pdf[1] and http://www.cdc.gov/vaccines/recs/provisional/downloads/pneumo-Oct-2008-508.pdf [31]

Timing of Vaccination

Pneumococcal vaccine should be given at least two weeks before elective splenectomy, if possible. For planning cancer chemotherapy or other immunosuppressive therapy (e.g., for patients with Hodgkin's disease or those who undergo organ or bone marrow transplantation), pneumococcal vaccination should be administered at least two weeks prior to the initiation of immunosuppressive therapy. Vaccination during chemotherapy or radiation therapy should be avoided. Based on literature reports, pneumococcal vaccine may be given as early as several months following completion of chemotherapy or radiation therapy for neoplastic disease. [32,33] In Hodgkin's disease, immune response to vaccination may be impaired for two years or longer after intensive chemotherapy (with or without radiation). During the two years following the completion of chemotherapy or other immunosuppressive therapy antibody responses improve in some patients as the interval between the end of treatment and pneumococcal vaccination increases. [32]
Persons with asymptomatic or symptomatic HIV infection should be vaccinated as soon as possible after their diagnosis is confirmed.

Use With Other Vaccines

The ACIP states that pneumococcal vaccine may be administered at the same time as influenza vaccine (by separate injection in the other arm) without an increase in side effects or decreased antibody response to either vaccine.[1] In contrast to pneumococcal vaccine, influenza vaccine is recommended annually, for appropriate populations. [34]

Revaccination

The ACIP has recommendations for revaccination against pneumococcal disease in persons at high risk who were previously vaccinated with PNEUMOVAX 23 or the pneumococcal conjugate vaccine. [1,31,35]
If PNEUMOVAX 23 is used for revaccination, a single 0.5 mL dose is administered subcutaneously or intramuscularly.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine. Epinephrine injection (1:1000) must be immediately available should an acute anaphylactoid reaction occur due to any component of the vaccine.

WARNINGS

For planning cancer chemotherapy or other immunosuppressive therapy (e.g., for patients with Hodgkin's disease or those who undergo organ or bone marrow transplantation), the timing of the vaccination is critical. (See INDICATIONS AND USAGE, Timing of Vaccination.)
If the vaccine is used in persons receiving immunosuppressive therapy, the expected serum antibody response may not be obtained and potential impairment of future immune responses to pneumococcal antigens may occur.[36] (See INDICATIONS AND USAGE, *Timing of Vaccination*.)
Intradermal administration may cause severe local reactions.

PRECAUTIONS

General

Caution and appropriate care should be exercised in administering PNEUMOVAX 23 to individuals with severely compromised cardiovascular and/or pulmonary function in whom a systemic reaction would pose a significant risk.

Any febrile respiratory illness or other active infection is reason for delaying use of PNEUMOVAX 23, except when, in the opinion of the physician, withholding the agent entails even greater risk.

In patients who require penicillin (or other antibiotic) prophylaxis against pneumococcal infection, such prophylaxis should not be discontinued after vaccination with PNEUMOVAX 23.

PNEUMOVAX 23 may not be effective in preventing pneumococcal meningitis in patients who have chronic cerebrospinal fluid (CSF) leakage resulting from congenital lesions, skull fractures, or neurosurgical procedures.

Routine revaccination of immunocompetent persons previously vaccinated with a 23-valent vaccine is not recommended. However, revaccination once is recommended for persons aged ≥ 2 years who are at highest risk for serious pneumococcal infections and those likely to have a rapid decline in pneumococcal antibody levels. (See INDICATIONS AND USAGE, *Revaccination*.)

Instructions to Health care Provider

The health care provider should determine the current health status and previous vaccination history of the vaccinee. (See INDICATIONS AND USAGE, *Revaccination*.)

The health care provider should question the patient, parent or guardian about reactions to a previous dose of PNEUMOVAX 23 or other pneumococcal vaccine.

Information for-Patients

The health care provider should inform the patient, parent or guardian of the benefits and risks associated with vaccination. For risks associated with vaccination, see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS. Patients, parents, or guardians should be told that vaccination with PNEUMOVAX 23 may not offer 100% protection from pneumococcal infection.

Patients, parents and guardians should be instructed to report any serious adverse reactions to their health care provider who in turn should report such events to the vaccine manufacturer or the U.S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967. [37]

Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with PNEUMOVAX 23. It is also not known whether PNEUMOVAX 23 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PNEUMOVAX 23 should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PNEUMOVAX 23 is administered to a nursing woman.

Pediatric Use

PNEUMOVAX 23 is not indicated in children less than 2 years of age.Safety and effectiveness in children below the age of 2 years have not been established. Children in this age group respond poorly to the capsular types contained in this polysaccharide vaccine. (See CLINICAL PHARMACOLOGY, Immunogenicity.)

Geriatric Use

Persons 65 years of age or older were enrolled in several clinical studies of PNEUMOVAX 23 that were conducted pre- and post-licensure. In the largest of these studies, the safety of PNEUMOVAX 23 in adults 65 years of age and older (n=629) was compared to the safety of PNEUMOVAX 23 in adults 50 to 64 years of age(n=379). The subjects in this study were ambulatory and had an expected prevalence of age associated chronic diseases. The clinical data did not suggest an increased rate or severity of adverse reactions among subjects ≥ 65 years of age compared to those 50 to 64 years of age. However, since elderly individuals may not tolerate medical interventions as well as younger individuals, a higher frequency and/or a greater severity of reactions in some older individuals cannot be ruled out. Post-marketing reports have been received in which some frail elderly individuals with multiple co-morbid conditions had severe adverse experiences and a complicated clinical course following vaccination.

ADVERSE REACTIONS

The most common adverse experiences reported with PNEUMOVAX 23 in clinical trials were:
Local reaction at injection site including soreness, erythema, warmth, swelling and induration
Fever ≤102°F
Other adverse experiences reported in clinical trials and/or in post-marketing experience with PNEUMOVAX 23 include:
General disorders and administration site conditions
Cellulitis
Asthenia
Malaise
Fever (> 102°F)
Chills
Pain
Decreased limb mobility
Peripheral edema in the injected extremity
Digestive System
Nausea
Vomiting
Hematologic/Lymphatic
Lymphadenitis
Lymphadenopathy
Thrombocytopenia in patients with stabilized idiopathic thrombocytopenic purpura[38]
Hemolytic anemia in patients who have had other hematologic disorders
Leukocytosis
Hypersensitivity reactions including
Anaphylactoid reactions
Serum Sickness
Angioneurotic edema
Musculoskeletal System
Arthralgia

† NOTE: The ACIP recommends routine vaccination for immunocompetent person 65 years of age and older

Arthritis
Myalgia
Nervous System
Headache
Paresthesia
Radiculoneuropathy
Guillain-Barré syndrome
Febrile convulsion
Skin
Rash
Urticaria
Erythema multiforme*Investigations*
Increased serum C-reactive protein

In post-marketing experience, injection site cellulitis-like reactions were reported rarely; between 1989 and 2002, when approximately 43 million doses were distributed, the annual reporting rate was <2/100,000 doses. These cellulitis-like reactions occurred with initial and repeat vaccination at a median onset time of 2 days after vaccine administration.

Systemic signs and symptoms including fever, leukocytosis and an increase in the laboratory value for serum C-reactive protein may be associated with local reactions.

In a clinical trial, an increased rate of local reactions has been observed with revaccination at 3-5 years following primary vaccination.

For subjects aged ≥65 years, it was reported that the overall injection-site adverse experiences rate was higher following revaccination (79.3%) than following primary vaccination (52.9%). For subjects aged 50-64 years, the reported overall injection-site adverse experiences rate for re-vaccinees and primary vaccinees were similar (79.6% and 72.8% respectively).

In both age groups, re-vaccinees reported a higher rate of a composite endpoint (any of the following: moderate pain, severe pain, and/or large induration at the injection site) than primary vaccinees. Among subjects ≥65 years of age, the composite endpoint was reported by 30.6% and 10.4% of revaccination and primary vaccination subjects, respectively, while among subjects 50-64 years of age, the endpoint was reported by 35.5% and 18.9% respectively. The injection site reactions occurred within the 3 day monitoring period and typically resolved by day 5.

The rate of overall systemic adverse experiences was similar among both primary vaccinees and revaccinees within each age group. The rate of vaccine-related systemic adverse experiences was higher following revaccination (33.1%) than following primary vaccination (21.7%) in subjects ≥65 years of age, and was similar following revaccination (37.5%) and primary vaccination (35.5%) in subjects 50-64 years of age. The most common systemic adverse experiences reported after PNEUMOVAX 23 were as follows: asthenia/fatigue, myalgia and headache.

Regardless of age, the observed increase in post vaccination use of analgesics (≤13% in the revaccinees and ≤4% in the primary vaccinees) returned to baseline by day 5.

DOSAGE AND ADMINISTRATION

Do not inject intravenously or intradermally

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. PNEUMOVAX 23 is a clear, colorless solution. The vaccine is used directly as supplied. No dilution or reconstitution is necessary. Phenol 0.25% has been added as a preservative.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of infectious agents from one person to another.

Withdraw 0.5 mL from the vial using a sterile needle and syringe free of preservatives, antiseptics and detergents.

Administer a single 0.5 mL dose of PNEUMOVAX 23 subcutaneously or intramuscularly (preferably in the deltoid muscle or lateral mid-thigh), with appropriate precautions to avoid intravascular administration.

Store unopened and opened vials at 2-8°C (36-46°F). All vaccine must be discarded after the expiration date.

Use With Other Vaccines

The ACIP states that pneumococcal vaccine may be administered at the same time as influenza vaccine (by separate injection in the other arm) without an increase in side effects or decreased antibody response to either vaccine.[1] In contrast to pneumococcal vaccine, influenza vaccine is recommended annually, for appropriate populations. [35]

HOW SUPPLIED

No. 4739 — PNEUMOVAX 23 is supplied as one 5-dose vial of liquid vaccine, color coded with a purple cap and stripe on the vial labels and cartons, NDC 0006-4739-00. No. 4739 — PNEUMOVAX 23 is supplied as one 5-dose vial of liquid vaccine, in a box of 10 five-dose vials, color coded with a purple cap and stripe on the vial labels and cartons, NDC 0006-4739-50. No. 4943 — PNEUMOVAX 23 is supplied as a single-dose vial of liquid vaccine, in a box of 10 single-dose vials, color coded with a purple cap and stripe on the vial labels and cartons, NDC 0006-4943-00.

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