

## Senior Lecture

## The pneumococcus: a round trip classic

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The isolation of *Streptococcus pneumoniae* (pneumococcus) was first reported in 1881 in independent studies by Pasteur<sup>1</sup> and Sternberg.<sup>2</sup> Few years later, Neufeld reported both the lytic action of ox bile on pneumococcal cultures<sup>3</sup> and the ‘Quellung’ (capsular) reaction.<sup>4</sup> These 2 tests together with the discovery of the characteristic optochin (Opt)-susceptibility of *S. pneumoniae*<sup>5</sup> still constitute the basis for the current clinical identification of the pneumococcus. Bile salts (i.e., sodium deoxycholate) trigger the peptidoglycan hydrolytic activity of *lytA* –the main pneumococcal autolysin–,<sup>6</sup> whereas Opt inhibits the  $F_0$  complex of the  $H^+$ -ATPase.<sup>7,8</sup> Besides, > 100 distinct capsule types (serotypes) have been described so far.<sup>9</sup> *S. pneumoniae* remains the leading cause of community-acquired pneumonia (CAP), meningitis, and bacteremia in children and adults and the most common cause of otitis media in infants and young children. In the preantibiotic era, i.e., before 1940, the mortality rate of pneumococcal CAP ranged 22.5–40.7%.<sup>10</sup> Nowadays, lower respiratory infections (LRI) rank fourth among all causes of death, and CAP alone produces more than a million deaths annually mainly in children younger than 5 years of age and adults  $\geq$  70 years of age. Of note, CAP accounts for  $\approx$  75% of the total deaths produced by lower respiratory tract infections (LRI).<sup>11</sup>

To date, antimicrobial resistance (AMR) is an increasingly serious threat to global public health that requires urgent action across all government sectors and society.<sup>12,13</sup> In Spain, near 2000 persons died in 2015 because of AMR according to a recent estimate;<sup>14</sup> this figure is higher than that caused by traffic accidents (<http://www.dgt.es/es/seguridad-vial/estadisticas-e-indicadores/publicaciones/anuario-estadistico-accidentes/>). Early investigations on pneumococci reported the first observations on the development of resistance *in vivo* to an antibacterial drug (Opt) in mice,<sup>15</sup> and then in man.<sup>16</sup> Resistance to sulfonamides, penicillin, and other drugs were reported many years later.<sup>17</sup> Currently, pneumococci are included as ‘medium priority’ in the WHO priority pathogens list for R&D of new antibiotics.<sup>18</sup> Importantly, multidrug-resistant (nonsusceptible to  $\geq$  3 classes of agents) and extensively drug-resistant (nonsusceptible to  $\geq$  5 classes) pneumococcal isolates account for 50% and 17%, respectively, in the Asia-Pacific region.<sup>19</sup> Novel and improved vaccines and investment in R&D to design new classes of antibacterials have been proposed as urgent instruments on the global action plan to tackle AMR (<http://www.emro.who.int/health-topics/drug-resistance/global-action-plan.html>). In this context, phage therapy –including phage lysins– are currently being tested in many laboratories including our own.<sup>20,21</sup>

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