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EC MICROBIOLOGY
Editorial

Brief History of *Staphylococcus aureus*: A Focus to Antibiotic Resistance

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Received: November 21, 2016; **Published:** January 05, 2017

Although the existence of staphylococci is as old as the age of earth, they were first identified as bacterial pathogen in 19th century. In 1880, Alexander Ogston first observed grape-like clusters of bacteria in pus from a surgical abscess in a knee joint and named them as *Staphylococcus* (Greek *staphyle*, "a bunch of grapes; *kokkos*, "grain or berry) [1]. In 1884, German physician Friedrich Julius Rosenbach was able to grow the organisms in pure culture and categorised them as per their colour production [1].

The foundation of antibiotic discovery was laid by Paul Ehrlich in 1906 with the discovery of compound 606, a gold powder, after the systematic screening approach including hundreds of derivatives of Atoxyl [2-4]. The compound was found effective for syphilis and released as *salvarsan* in 1910 [5]. Salvarsan and its derivative neosalvarsan were prescribed frequently until the introduction of penicillin in the 1940s [5].

Alexender Fleming accidentally discovered penicillin in 1928 in environmental mold, *Penicillium notatum*, contaminating the pure culture of *Staphylococcus aureus* [6]. The pure penicillin compound from the mould was successfully extracted in 1939 by Howard Walter Florey and Ernst Boris Chain [7]. With its first clinical use in 1941 [8], the antibiotic penicillin was initially kept limited to the soldiers in World War II [9]. The drug was proven so effective in the treatment of several bacterial infections that in a short time it earned the reputation as a '*magical bullet*' or a '*miracle drug*' [9].

After the end of war, other types of penicillin were developed and produced in large-scale by the European pharmaceutical companies [2,9]. Varieties of novel antibiotics of different classes were developed between 1950s and 1970s, a period referred to as antibiotic era or golden era of antibiotic discovery [2,3].

Surprisingly, a year earlier to the first clinical use of penicillin, the penicillin-resistant *S. aureus* report was published in 1940 [10]. It is an interesting reminder that Fleming had predicted this event in 1945 [11] "*But I would like to sound one note of warning…. It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body*".

Resistance to this wonder drug spread rapidly and methicillin was developed in 1959 at Beecham, British Pharmaceutical Company as first semi-synthetic penicillin to treat infections caused by penicillin-resistant *Staphylococcus aureus* [12]. Methicillin was believed to stop the existence of the resistant staphylococcus and Ernst Chain told in its favour "*no more resistance problems, methicillin is the answer*" [12]. The methicillin resistant *Staphylococcus aureus* (MRSA) strains were detected in 1961 [13,14]. The infections of *S. aureus* became a challenging threat when the strains of MRSA were noticed with multiple drug resistance (MDR) in the late 1970s [15,16].

Vancomycin was discovered in 1953 by Edmund Carl Kornfeld [17]. It was aimed to act on the strains unresponsive to methicillin and got U.S. Food and Drug Administration (FDA) approval in 1958 [18]. The first strain of *S. aureus* with reduced susceptibility to vancomy-

cin; vancomycin intermediate *S. aureus* (VISA), was isolated in 1996 from a Japanese patient [19]. The first clinical isolate of vancomycin resistant *S. aureus* (VRSA) was reported from United States in 2002 [20].

The option to combat infections with VRSA and VISA infections is linezolid, the oxazolidinone antibiotic, approved by FDA in year 2000 [21]. The first case of linezolid-resistant staphylococci appeared in 2001 [22]. Although linezolid appears promising to treat *S. aureus* infections, it has been reported resistant from some parts of geographical regions [23]. Khan., *et al*. published first report of India from Chattisgarh state for finding two clinical isolates of linezolid resistant MRSA in March 2011 from pus samples [24].

With limited choice of antimicrobials, MRSA infections are difficulty-to-treat and associated with significant increase in morbidity, mortality and hospital cost [25-27]. In preantibiotic era, the peoples dying of *S. aureus* infection were as high as 82 percent [30]. Penicillin saved many lives after its first introduction in market. But at present, about >80% *S. aureus* infection cases are unresponsive to penicillin therapy. The historical milestones reveal a long journey of antibiotic discovery but a relatively short time taken by *S. aureus* to acquire the drug resistance. Penicillin discovery took dozen years patience to its extraction in pure form whereas penicillin resistant strain was reported a year earlier to its first therapeutic use [2,3,7]. On the development of methicillin for penicillin resistant bacteria, it was believed to be the end of the resistant staphylococcus. The two decades duration from the first report of penicillinase-producing *S. aureus* to the first market availability of methicillin drug was ruined shortly with the report MRSA isolates in 1961 [13]. Vancomycin was the antibiotic developed earlier to methicillin but it could not pass "more effective and less toxic" criterion for its approval before methicillin. Vancomycin was approved in 1958 in an event of increase in MRSA cases. VISA and VRSA has become a global issue which require the use of linezolid antibiotic for the treatment. The threatening reports of emergence of resistance to linezolid and even newer antimicrobial agents pave the way to post-antibiotics era [29,30].

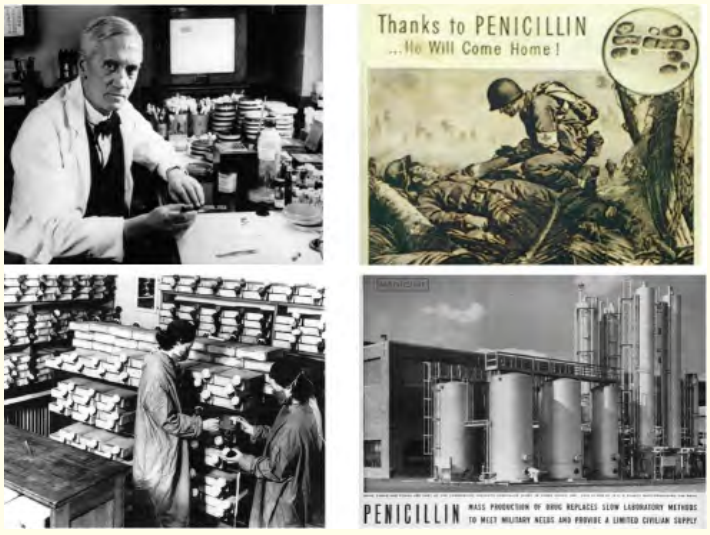

Figure: *Upper left; Alexander Fleming (1881–1955) in his laboratory. Upper right; World War II poster. Lower left; Production of penicillin in bedpans during the first years of the World War II. Lower right; Production of penicillin at the end of the World War II.*

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