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EVOLUTION OF *BORDETELLA PERTUSSIS* UNDER THE INFLUENCE OF VACCINATION AND ITS MOLECULAR-GENETIC PROPERTIES

In recent decades, there has been a global trend of increasing incidence of pertussis and changes in its epidemiological characteristics toward re-emergent properties. This trend has become especially pronounced in the post-COVID-19 pandemic period in the European Region (87,558 cases in 2023), including Ukraine (7,545 cases in 2024). One of the reasons for this situation is considered the introduction of the acellular pertussis vaccine (aP) in some countries, due to its shorter duration of post-vaccination immunity and the loss of certain antigens by circulating Bordetella pertussis strains under the pressure of specific post-vaccination antibodies. However, in Ukraine, the whole-cell pertussis vaccine (wP) is currently used for routine immunization. The ***aim*** *of this work is to summarize scientific information on the biological properties of B. pertussis circulating in different regions and formed under the influence of aP and wP vaccines. The virulence factors of B. pertussis are analyzed, including those with antigenic properties used in aP vaccines. An analysis of existing scientific data on the molecular-genetic and antigenic characteristics of B. pertussis variants using aP and wP vaccines was carried out. It is* ***concluded*** *that long-term vaccination against pertussis, on the one hand, leads to a sharp decrease in the incidence of this infection, and on the other hand, contributes to the further evolution of B. pertussis, promoting changes or loss of certain antigens and further genetic distance from vaccine strains of both aP and wP types. This allowed the pathogen to evade specific immunity at both the individual and population levels and caused an increase in incidence. The aP vaccines accelerate such evolutionary changes to a greater extent. At the same time, the genetic diversity of variants in territories using aP vaccines is greater compared to those using wP (which may even be limited to clonal variants). A trend is observed toward increasing similarity of B. pertussis strains circulating worldwide.*

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This may be due to the same direction of evolutionary changes and intensive population migration processes, which turn the globe into a single epidemic zone. One of the negative trends is the emergence of macrolide-resistant B. pertussis variants, which are widespread in China and still sporadically observed in Europe. All of the above contribute to the loss of vaccine controllability of pertussis and the emergence of a tendency to transition at this stage to re-emergent infections. This requires the widespread implementation of molecular-genetic monitoring in the epidemiological surveillance of pertussis and the improvement of vaccination strategy and tactics based on its results.

***Keywords**: B. pertussis, molecular-genetic properties, antigens, acellular vaccine, whole-cell vaccine, vaccine prophylaxis, re-emergent infection.*

Despite many years of pertussis vaccination and significant achievements in reducing the incidence of this infection worldwide in the post-vaccination period through the use of whole-cell pertussis vaccines (wP), recent decades have shown a trend toward increasing incidence and changing epidemiological characteristics of the disease. While global incidence in the pre-pandemic period (2010—2019) ranged from 149,845 to 250,330 cases per year, in the European Region — from 28,212 to 60,402 (*WHO, 2010—2023*), and in Ukraine — from 686 to 2,937 cases annually, a sharp decline was observed during the COVID-19 pandemic (2020—2022). This decrease was due to the implementation of epidemic control measures, which significantly reduced the activity of the droplet transmission mechanism (Fig. 1, 2).

Subsequently, a sharp rise in incidence was observed, surpassing pre-pandemic levels in the European Region (87,558 cases in 2023) and exceeding the figures of the previous 30 years in Ukraine (7,545 cases in 2024). The discussion about the causes of this re-emergence of a disease long considered vaccine-preventable has been ongoing for some time. One of the widely considered factors is the introduction of the acellular pertussis vaccine (aP) in several countries, which provides shorter-lasting post-vaccination immunity and may have contributed to the loss of certain *Bordetella pertussis* antigens due to selective pressure from vaccine-induced antibodies. This issue requires thorough investigation, as it directly impacts the future of pertussis vaccination strategies and the ability to control the epidemic process.

In view of the above, the **aim** of this study is to summarize scientific information on the biological properties of circulating *B. pertussis* strains in different regions, shaped by the use of acellular and whole-cell pertussis vaccines.

B. pertussis and its virulence factors. Bordetella pertussis belongs to the genus *Bordetella* within the family *Alcaligenaceae*. Humans are the only biological hosts of this pathogen. The virulence factors of *B. pertussis* are presented in the Table (Zadorozhna & Doan, 2004; Kilgore et al., 2016; Teruya et al., 2020; Burnham-Marusich et al., 2020). As seen, many of them are important for the immune response, being part of the wP or aP vaccines, and can also change the properties of pathogen variants circulating in certain territories.

B. pertussis, a highly contagious pathogen restricted to a single host species — humans — evolved from a common ancestor shared with *Bordetella parapertussis* and *Bordetella bronchiseptica*. Having lost the ability to survive outside its biological host, *B. pertussis*, in the process of adapting its metabolism to a specific ecological niche, developed tightly regulated virulence factors. Today, in order to persist as a species, the pathogen must also evade post-vaccination immunity — a challenge it meets through newly emerging adaptive mechanisms (Belcher et al., 2021). *B. pertussis* strains that have lost the ability to produce antigens such as pertactin (prn), pertussis toxin (ptx), filamentous hemagglutinin (FHA), fimbriae types 2 and 3 (fim2 and fim3), and tracheal colonization factor (tcfA) have been isolated in countries with high vaccination coverage. This may be related either to the natural evolution of *B. pertussis* or to adaptive mechanisms that enable the pathogen to persist in vaccinated populations. Most of the described mutants were

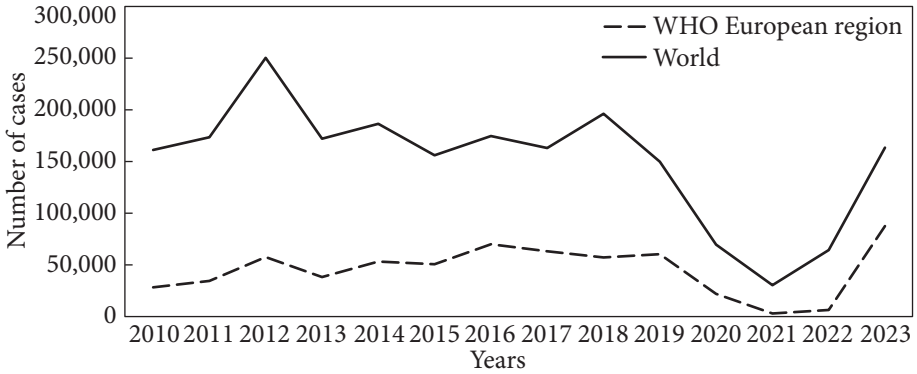

Fig. 1. Pertussis incidence in the world and the WHO European Region (2010—2023)

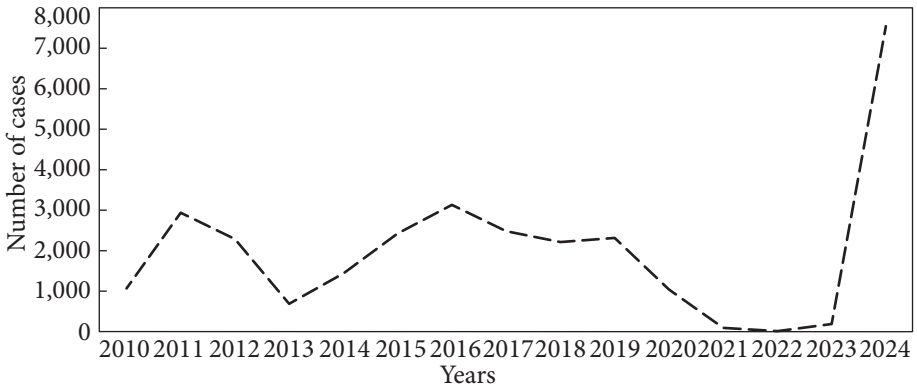

Fig. 2. Incidence of whooping cough in Ukraine (2010—2024)

Table 1. ***B. pertussis*** **virulence factors** (Kilgore et al., 2016; Teruya et al., 2020; Burnham-Marusich et al., 2020)

Virulence factor	Structure	Localization	Functions and role in immunity
ptx (pertussis toxin)	Consists of 5 subunits (94 kDa): ADP-ribosylating exotoxin type AB5, A (S1) catalytic subunit, and B (S2 to S5) subunits	Periplasm	Production of functional ptx is unique to *B. pertussis*; S1 subunit, ADP-ribosyltransferase (G protein ribosylation); subunits S2 to S5 bind target cell receptors; increases histamine sensitivity, induces lymphocytosis and insulin secretion, and alters T-cell response; toxoid is a component of aP vaccines
AC (adenylate cyclase)	Two functional C- and N-terminal domains (25 and 18 kDa, respectively); activated by calmodulin and generates cAMP	Extra-cytoplasmic	Binds target cells via C-terminal domain; converts ATP to cAMP via N-terminal domain; enzymatically active hemolysin; inhibits migration and activation of phagocytes; blocks induction of bactericidal nitric oxide in macrophages; inhibits cytotoxic activity of neutrophils, monocytes, and natural killer cells; inhibits T-cell activation and chemotaxis; natural infection and wP vaccination induce antibodies to AC

Continuation of Table 1

Virulence factor	Structure	Localization	Functions and role in immunity
DNT (dermanecrotic toxin)	Needle-shaped structure; proteins secreted by the T3SS include Beta A, BopN, BopD, and Bsp22	Cell membrane	Translocates effector proteins in host cells, induces cell necrosis *in vitro*, disrupts innate and adaptive immune responses during lung infection; Beta A cytotoxicity in vitro (mechanism not well understood); BopN, turns off host inflammatory response. Probably the cause of whooping cough encephalopathy
TST (tracheal cytotoxin)	Disaccharide-tetrapeptide peptidoglycan monomer (9.2 kDa)	Extracellular space	Produced during cell wall remodeling, acts synergistically with lipopolysaccharide toxin to stimulate the production of pro-inflammatory cytokines (TNF-α, IL-1α, IL-1β, and IL-6), induces nitric oxide synthase to produce nitric oxide, and damages ciliated cells; thought to cause whooping cough and/or coughing paroxysms. Not involved in immune response
FHA (filamentous hemagglutinin)	Filamentous, surface-associated and secreted protein (220 kDa); heparin binding domain, Arg-Gly-Asp and Chinese hamster ovary recognition domain; FHA and filamentous hemagglutinin transporter protein (FhaC) function as prototypes of secretory pathways	Cell wall	Carries out the initial adhesion of B. pertussis to the ciliated epithelium of the upper respiratory tract; is required for the progression of infection from the upper to the lower respiratory tract; promotes phagocytosis of *B. pertussis* by macrophages and polymorphonuclear neutrophils; induces the release of IL-6 and IL-10; inhibits the production of IL-12 by macrophages and dendritic cells. Antibodies against FHA are transferred transplacentally
fim (fimbriae) (type I pili)	Fim types 2 and 3 products present serotype-specific AGG; fim strains are sensitive to variation and polymorphism; fimD antigen is common to all fimbriae	Surface protrusions	Fim 2 and 3 are essential components for colonization of the lower respiratory tract mucosa, involved in attachment and suppression of the initial inflammatory response to infection; AGG is present in all whole-cell vaccines; fim antigens may be present in small amounts in acellular vaccines
prn (pertactin)	The autotransporter protein mediates eukaryotic cell binding via an Arg-Gly-Asp motif, highly immunogenic, highly polymorphic (69 kDa)	Surface	Resists neutrophil-mediated clearance; promotes attachment of B. pertussis to ciliated respiratory epithelium in rabbits; changes in prn types have resulted in less effective whole-cell vaccine; prn2 and prn3 are the most common circulating types of prn strains; prn1 antigen is present in many acellular vaccines; antigenic variation of prn in vaccines is implicated in loss of immunity to *B. pertussis*
tcfA (tracheal colonization factor A)	Autotransporter protein (60 kDa)	Superficial, secretory	Tracheal colonization. Can be used as a biomarker for early diagnosis
Lipopolysaccharide	Endotoxin	Surface	Causes fever after administration of wP vaccines; antigenic and adjuvant properties, but not protective; not a component of aP vaccines
BrkA, BapC, BatB, Vag8, SphB1, Phg	BvgAS-activated classical transport proteins; BrkA (73 kDa) for the N-terminal domain and 30 kDa for the C-terminal outer membrane protein; Vag8 (95 kDa)	Surface	Mediates binding, counteracts complement, avoids antibody-mediated clearance and proteolytic processing of other surface proteins; SphB1 is required for FHA maturation; BrkA is a bactericidal resistance factor

characterized by a lack of prn production. Such isolates have been identified in countries using aP vaccines. Prn-negative (prn-) strains were isolated from patients exhibiting classic clinical symptoms of pertussis, similar to those caused by prn-positive (prn+) variants. In both *in vitro* and *in vivo* studies, (prn-), (ptx-), and (FHA-) isolates retained cytotoxic properties and, except for isolates (ptx+), were lethal to mice infected intranasally (Polak & Lutyńska. 2017).

This requires further study of the significance of certain virulence factors of the pathogen in the pathogenesis of pertussis and consideration of associated features when improving vaccines and vaccine prophylaxis for this infection. In addition, a deep understanding of the evolutionary trends of *B. pertussis* under the influence of wP and aP vaccines and their differences is necessary.

Characteristics of B. pertussis variants circulating in countries using aP vaccines. Unfortunately, molecular-genetic monitoring of circulating *B. pertussis* strains is not systematically conducted in individual countries and is often limited to isolated research studies. As a result, it is difficult to form a complete and reliable picture of the pathogen's evolutionary changes. Nevertheless, these individual studies do reveal certain trends.

African Region. A genomic analysis of *B. pertussis* strains from South Africa (32 isolates, 2015—2019), which switched to aP vaccines in 2009, revealed genetic homogeneity. The dominant genotype with respect to vaccine antigens was ptxP3-ptxA1-ptxB2-prn2-fimH2, accounting for 96.9% of isolates. Unlike findings in other countries, there was no evidence of mutations in genes encoding antigens included in aP vaccines. Based on this, the authors concluded that the observed increase in pertussis cases may be driven by other factors — such as the cyclical nature of the disease, waning immunity due to aP vaccine use, and/or immunity gaps within the population — all of which warrant further investigation (Moosa et al., 2023).

American Region. In the United States, where the aP vaccine is used, more than 85% of *B. pertussis* isolates were already pertactin-deficient (prn-) over a decade ago. Notably, the proportion of patients reporting individual pertussis symptoms was similar in both (prn-) and (prn+) groups. However, a greater proportion of patients infected with (prn+) strains reported apnea, while those who had received at least one dose of pertussis vaccine were more likely to become sick when infected with a (prn-) *B. pertussis* strain, compared to unvaccinated individuals (Martin et al., 2015). This finding requires further analysis to better understand the underlying causes. In another US study, the disease duration was shorter among patients infected with prn-deficient *B. pertussis* (with a mean difference of 3.2 days), although no significant difference was found in infants under 4 months of age (Vodzak et al., 2017). The discovery that most circulating *B. pertussis* strains in the U.S. have acquired new independent disruptive mutations in the prn gene serves as strong evidence of intense selective pressure from post-vaccination antibodies. However, for the other four antigens included in the aP vaccine, genetic selection has not occurred as rapidly. The authors identified three key aspects of prn that may help explain the rapid loss of this antigen by the bacteria: (1) its functional redundancy; (2) the relatively longer persistence of anti-pertactin antibodies; and (3) its proximity to the outer membrane, making it more accessible for complement fixation (Ma et al., 2021).

In Canada, a longitudinal study conducted between 1994 and 2013 showed that the first (prn-) strains appeared only in 2012, accounting for 17.8% of all *B. pertussis* isolates that year. Importantly, this was not the result of the spread of a single genetic clone, but rather multiple independent genetic events that led to the emergence of (prn-) variants. By 2016, the prevalence of (prn-) strains had increased to 70.8%, although a decline was observed in 2017, with (prn-) strains comprising 46.2% of isolates (Tsang et al., 2014; Tsang et al., 2019).

In Mexico, the aP vaccine was introduced in 2007. A study of *B. pertussis* strains isolated from patients between 2006 and 2014 identified one dominant endemic clone (clone A, 55%) and three main subtypes (A1, A2, and A3). All isolates carried the allelic combination ptxP3-ptxA1. These corresponded to novel genotypes ptxP3-ptxA1-prn2-fim2-1-fim3-2 and ptxP3-ptxA1-prn2-fim2-1-fim3-1, which are characterized by global dissemination and association with pertussis outbreaks (Gutiérrez-Ferman et al., 2018). Similar findings were reported in other studies in the same period (Rodríguez-Medina et al., 2023).

European Region. European countries, exept Poland, replaced wP vaccines with aP vaccines back in the 1990s. An analysis of the genetic characteristics of 466 *B. pertussis* isolates collected between 1998 and 2012 from 13 European countries demonstrated a highly similar *B. pertussis* population in 12 countries using aP vaccines, whereas Polish strains showed considerable genetic differences. Thus, this study suggested that the use of aP versus wP vaccines results in the formation of distinct *B. pertussis* populations (van Gent et al., 2015). Further research conducted in Poland confirmed this hypothesis. Sequence analysis of the ptxA, ptxC, prn, tcfA, fim2, fim3, and ptxP genes was performed for 175 clinical *B. pertussis* isolates circulating in Poland since 1959, alongside vaccine strains used currently and previously. Clinical isolates in 1995—2013 differed from the three vaccine strains currently in use, which carry allelic combinations ptxA2-ptxC1-ptxP1-prn1-tcfA2-fim2-1-fim3-1, and which were frequently detected in Poland at the onset of pertussis vaccination but have not been observed since 1995. Among isolates of 2000—2013, two genotypes predominated: ptxA1-ptxC1-ptxP1-prn1-tcfA2-fim2-2-fim3-1 and ptxA1-ptxC1-ptxP1-prn2-tcfA2-fim2-1-fim3-1 (45% and 32.5%, respectively). Isolates with the profiles ptxA1-ptxC2-ptxP3-prn2-tcfA2-fim2-1-fim3-2 and ptxA1-ptxC2-ptxP3-prn2-tcfA2-fim2-1-fim3-1, which are now widespread in other EU countries, were rarely detected in Poland during the same period, with frequencies of 10% and 5%, respectively. The authors suggest that several previous changes in the composition of the wP vaccine produced and used in Poland led to more diverse immune pressure in the population, resulting in a different prevalence of alleles compared to other regions (Mosiej et al., 2015). Currently, Poland employs the wP vaccine for the primary immunization series and the first booster dose, with the aP vaccines used starting from 6 years of age (ECDC, 2025).

A revealing study was conducted in Sweden, where the pertussis immunization strategy changed drastically over time (until 1979 — wP vaccine, 1979—1996 — a 17-year period without vaccination, and since 1997 — aP vaccine). The population of 1,247 *B. pertussis* strains was characterized according to these periods (the study ended in 2003), with serotyping and genotyping for prn and ptxA performed. Throughout this period, the vast majority of strains were of the non-vaccine type and changed in their serotypes corresponded to the vaccination program shifts. Isolates of serotype fim3 were most common during vaccination periods, whereas serotype fim2 predominated during the 17-year no-vaccination interval. Strains with prn1 dominated during wP vaccination but were later replaced by prn2 strains, which were no longer detected after the introduction of aP vaccine**s**. Strains with ptxA1 prevailed throughout all three decades. Regarding dominant serotypes identified by pulsed-field gel electrophoresis, fim3 prn1/7 and fim3 prn2 were detected during the wP vaccine period, fim2 prn2 during the no-vaccination period, and fim3 prn2 — after aP vaccine implementation. However, despite the observed differences among circulating pathogen variants, the authors did not perceive any threat of bacterial polymorphism impacting the effectiveness of the vaccination program (Hallander et al., 2005).

Among 11 strains isolated in Europe in 1999—2012 (Netherlands — 6 strains, Norway — 1, France — 2, Sweden — 2), all carried the ptxP3

allele; 5 were pertactin-negative (prn-), 2 were FHA-negative (FHA-), and one strain was both (prn-) and (FHA-) (*Bart et al., 2015*). The evolution of *B. pertussis* in Norway was traced from 1996 to 2019. A total of 22 isolates from the wP vaccine period (1996—1997) and 158 from the aP vaccine period (1998—2019) were analyzed. Seven distinct allele profiles (A-F) of aP genes were identified, with profiles A1, A2, and B predominating (89%), all carrying ptxA allele 1, ptxP promoter allele 3, and prn allele 2. Isolates with ptxP1 and prn1 alleles were not detected after 2007, while the prn2 allele likely emerged before 1972, and ptxP3 before the early 1980s. Allelic conversions of aP genes occurred before vaccine introduction. Mutations in the prn gene were found in 16% of isolates. The aP vaccine and its booster doses (introduced for children in 2007 and for adolescents in 2013) may have contributed to the emergence of a more homogeneous *B. pertussis* population characterized by ptxA1, ptxP3, and prn2 alleles, alongside an increasing number of prn mutations. These strains differ from aP vaccine strains (ptxA1, ptxP1, prn1) (Brandal et al., 2022), which have implications for vaccine effectiveness.

In Finland, the aP vaccine without the fim antigen was introduced in 2005. To determine the dynamics of genetic changes in *B. pertussis*, strains isolated from 1974 to 2023 were studied. During the use of the wP vaccine, most circulating *B. pertussis* belonged to the fim2 serotype. However, from 1999, variants with fim3 appeared and begun to spread. After the introduction of the aP vaccine, the distribution of serotypes showed considerable variability. Moreover, fim3 isolates demonstrated enhanced biofilm formation compared to fim2 isolates. Additionally, this ability was more pronounced among fim3 isolates with the fim3-2 allele compared to fim3-1 (*Niinikoski et al., 2024*). Among 462 characterized *B. pertussis* isolates, one was resistant to macrolides. It had the fim2 serotype, pertactin (prn) deficiency for the vaccine antigen, and contained the ptxP3 allele. The authors expressed concern about the emergence of macrolide-resistant *B. pertussis* (MRBP) in Europe and emphasized the importance of its rapid identification (Miettinen et al., 2024).

In Slovenia, aP vaccines containing prn were mostly used over 1999—2016, and aP without prn — since 2017. Among 123 B. pertussis strains isolated in 2002-2020, 48 were prn-deficient; of these, 44 were isolated after 2017 (Barkoff et al., 2024). Although the authors conclude that changes in the aP vaccine may increase the number of cases of pertussis caused by prn-deficient *B. pertussis*; these variants are likely the result of the establishment of those that emerged during the use of previous vaccines.

In France, as in other European countries, in 2024, pertussis increased. Between 1 January and 31 May, 5616 (24.9%) positive PCR tests for *B. pertussis* were detected after 3 years of almost no infection. Among the 67 strains sequenced, 66 produced prn and 56 — fim2, in contrast to the pre-COVID-19 period. One isolate of the Bp-AgST4 genotype was found to be MRBP (Rodrigues et al., 2024), which, together with reports from other countries, indicates the risks of further spread of such pathogen variants in Europe.

7 isolates isolated in 2023 in Spain showed the same allelic combination ptxA1/ptxP3/prn2/fim2-1/fim3-1, and all of them expressed prn (Marimón et al., 2024).

Western Pacific Region. Japan was the first to introduce the aP vaccine. Whole-genome sequencing of strains collected between 1982 and 2014 revealed that the *B. pertussis* population in Japan consisted of two main clades that split over 40 years ago. About 20% of these strains showed alterations in the prn gene, caused by either a deletion in the signal sequence (ΔSS) or insertion of IS element IS481. Phylogenetic analysis pointed to Japan as the origin of the parental clones for these isolates. The first generation of prn-deficient mutants was traced back to around 1990 in Japan, and it was demonstrated that strains harboring the alternative prn2 allele

might have emerged there around 1974 coinciding with changes in the vaccine strategy in the country (Zomer et al., 2018).

During the 2008—2012 pertussis epidemic in Australia, (prn-) variants also appeared. Their spread continued through 2013—2017, mainly among ptxP3 strains. Additionally, a strain lacking both (FHA-) and (prn-) was identified. Further investigations revealed that the Australian *B. pertussis* population is dominated by ptxP3 strains with various fim3 alleles, with the ptxP3-fim3A genotype significantly more widespread than the ptxP3-fim3B genotype. The authors' relative risk analysis suggested that after a new *B. pertussis* lineage emerges, it tends to have a local impact during its first 1.5 years before spreading more broadly. Phylogenetic data further linked the expansion of ptxP3 strains to the replacement of the type III secretion system allele bscI1 by bscI3. The bscI3 allele is associated with reduced T3SS secretion, potentially allowing *B. pertussis* to evade immune detection. These findings deepen our understanding of the spatial and temporal dynamics of *B. pertussis* in highly vaccinated populations and their influence on epidemic trends (Xu et al., 2019; Xu et al., 2022).

Acellular vaccines began to be introduced in China starting in 1995 (Wang, Lei & Zhang, 2012). Chinese researchers attempted to explain the paradox of a decline in pertussis cases among infants alongside an increase in fatal outcomes by the rise in circulation of erythromycin-resistant *B. pertussis* (ERBP). The ptxP3 variant of *B. pertussis* was found to be more virulent than ptxP1. In China, erythromycin-sensitive ptxP3 strains were identified from 2002, while the first erythromycin-resistant ptxP3 strain (ERBP-ptxP3) was detected in 2017. Between 2020 and 2022, the ERBP-ptxP3 variant displaced the ptxP1-expressing ERBP-ptxP1 strain. In 2019, ERBP-ptxP1 accounted for 91.6% of pertussis cases, with no ERBP-ptxP3 detected; conversely, by 2022, the proportions shifted dramatically to 19.6% ERBP-ptxP1 and 80.4% ERBP-ptxP3. ERBP-ptxP3 demonstrated a stronger ability to evade immune selection pressure. All 44 *B. pertussis* isolates collected in Beijing over 2022—2023 belonged to ERBP-ptxP3, among which two lacked the vaccine antigen FHA, 30 were prn-deficient, and one lacked multiple immunogens. This situation impacts both patient treatment and the overall efficacy of pertussis vaccination. To address the rising prevalence of ERBP-ptxP3, the authors emphasize investigating alternative antibiotic options, optimizing vaccination schedules for lifelong comprehensive protection, or targeted strategies to ensure specific immunity in neonates. Various program options are currently under consideration in China (Du et al., 2024). Subsequent studies analyzing the whole genome of 60 strains isolated in Beijing from 2020 to 2023 assessed the genetic evolution of *B. pertussis* through key virulence genes (ptxP, ptxA, prn, fim2, fim3, and tcfA) and the A2047 locus associated with ERBP. The dominant antigenic genotype was ptxP3/prn2/ptxA1/fim2-1/fim3-1/tcfA2 (88.3%), differing from the previously prevalent genotype ptxP-1/prn-1/ptxA-1 in Beijing before 2019 and the vaccine strain genotype ptxP-1/prn-1/ptxA-2/fim2-1/fim3-1/tcfA2. Significant genetic changes linked to vaccine introduction were identified, particularly in the acellular vaccine era. Initially, common genotypes were ptxP-1, prn-1, ptxA-2, fim2-2, and fim3-2; however, ptxP-3, prn-2, and ptxA-1 have now become globally dominant, indicative of vaccine-driven selection pressure. Additionally, all strains harbored the A2047G mutation, with 91.7% belonging to ptxP3. The authors conclude that the prevalence of ERBP-ptxP3 may continue to rise (Li et al., 2025). An investigation of 442 *B. pertussis* strains across 7 antigen genotypes (ptxA, ptxC, ptxP, prn, fim2, fim3, tcfA), isolated in Northern China between 2019 and 2023, showed an increase in highly virulent ptxP3-containing strains from 13.5% in 2019—2021 to 93.0% in 2022—2023. Concurrently, the proportion of ERBP-ptxP3 rose from 42.9% to 100%. 76% of

ptxP3 isolates had genotype ptxA1/ptxC1/prn2/fim2-1/fim3A/tcfA-2. Among patients, children aged 3—14 years represented 13.5% in 2019, increasing to 45.6% in 2023. 66% of strains were classified as the MT28 type by multilocus tandem-repeat analysis, with 87.9% being ERBP. All sequenced ERBP-ptxP3 strains belonged to sublineage IVd. These data indicate that clonal dissemination of highly virulent, macrolide-resistant ERBP-ptxP3 *B. pertussis* may be a key factor in the recent pertussis resurgence in China (Hu et al., 2025). Studies of *B. pertussis* strains isolated in Shanghai concerning the A2047G gene mutations demonstrated that the proportion of resistant strains increased from 36.4% (2016) to 97.2% (2022). The predominant genotypes were ptxP1/prn1/fhaB3/ptxA1/ptxC1/fim2-1/fim3-1 (48.7%) and ptxP3/prn2/fhaB1/ptxA1/ptxC2/fim2-1/fim3-1 (47.7%). All MRBP *B. pertussis* strains before 2020 carried ptxP1, with 51.4% belonging to the MT type, whereas the proportion of ptxP3-MRBP increased from 0% before 2020 to 66.7% after 2020, all classified as MT28. The emergence and spread of MT28 ptxP3-MRBP strains are likely linked to the A2047G mutation and selection pressure imposed by vaccination and widespread macrolide use, further complicating the epidemiological landscape and posing a threat to global public health (Fu et al., 2024).

Characteristics of circulating B. pertussis variants in countries using whole-cell pertussis vaccines. Shifts in circulating *B. pertussis* variants are observed not only in countries using aP vaccines but also in regions where wP vaccines have been used consistently for many years. Unfortunately, research data on pathogen evolution in such settings remain limited to only a few countries. The characteristics of isolates obtained in Poland and Sweden, analyzed comparatively in the context of immunoprophylaxis strategy changes, were discussed earlier.

In Peru, genetic analysis of *B. pertussis* strains identified during the 2012 pertussis epidemic revealed two clonal groups corresponding to genotypes already recognized globally at the time: ptxP3-ptxA1-prn2 or 9-fim3-1 and ptxP3-ptxA1-prn2 or 9-fim3-2. The authors emphasized that low vaccination coverage (<50%) and genetic divergence between vaccine strains and local isolates may have contributed to the increased pertussis incidence (Bailon et al., 2012).

In Brazil, an elevated incidence of pertussis was recorded between 2012 and 2018, despite high vaccination coverage. Genotyping of 136 strains by ptxP and fim3 revealed that the most prevalent variant was fim3-24/ptxP3 (68%), which was associated with the peak in pertussis cases. Two additional genotypes were also identified: fim3-1/ptxP3 (15%) and fim3-3/ptxP3 (17%). Notably, strains corresponding to the wP vaccine genotype (Bp137) — fim3-1/ptxP2 — were not detected (de Paula et al., 2024). A similar trend has been observed in Argentina. A molecular characterization study of *B. pertussis* isolates collected in Buenos Aires from 2000 to 2017 showed that 90.6% of the strains carried the allele profile ptxP3-ptxA1-prn2-fim3-2. Only two isolates were pertactin-deficient, which the authors attributed to a greater influence of aP vaccines on prn gene expression loss compared to wP vaccines (Carriquiriborde et al., 2019).

In Iran, which has a more than 50-year history of using wP vaccines and maintains approximately 95% vaccination coverage, analysis of *B. pertussis* strains isolated between 2008 and 2016 revealed that the majority (76%) carried the ptxP3/prn2 alleles — genotypes similar to those circulating in countries employing aP vaccines. A subsequent study of strains collected between 2005 and 2017 demonstrated a continuous increase in the population of ptxP3/fim3-2 *B. pertussis* isolates, which were differentiated into nine distinct clades. Furthermore, the first ptxP3 *B. pertussis* isolates lacking FHA expression — a key antigen and major component of aP vaccines — were identified. These findings suggest that *B. pertussis* continues to evolve and adapt, regardless of the type of vaccine used (Safarchi et al., 2019; Safarchi et al., 2021).

In India, analysis of two clinical isolates from 2017 collected after years of exclusive wP vaccine use identified insertion elements flanked by IS481, which are considered significant in bacterial genome evolution. These *B. pertussis* strains exhibited genomic diversity relative to Indian wP vaccine reference strains. They also contained multiple virulence-associated genetic elements and pertussis toxin subunits, classified as sequence type ST2 (Sharma et al., 2021).

According to a recent comprehensive review, researchers suggest that clinical symptoms and disease severity of pertussis appear comparable whether caused by (prn-) or (prn+) *B. pertussis* strains. The authors emphasize that there is currently no evidence of compromised aP vaccine protection in countries where (prn-) strains dominate the circulating *B. pertussis* population (Heininger et al., 2024).

Conclusions. Decades of pertussis vaccination, on the one hand, have led to a dramatic reduction in disease incidence, but on the other hand, have driven the ongoing evolution of *B. pertussis*. This evolution has manifested itself in antigenic variation or loss and increasing genetic divergence from both aP and wP vaccine strains. As a result, *B. pertussis* has gained the capacity to evade specific immunity at both individual and population levels, contributing to the resurgence of pertussis cases. Acellular vaccines appear to exert stronger selective pressure, accelerating such evolutionary changes. Consequently, greater genetic diversity of circulating *B. pertussis* strains is observed in regions using aP vaccines compared to those using wP vaccines, where the diversity may be limited to a few clonal variants. At the same time, there is a global trend toward increasing similarity among circulating *B. pertussis* strains, likely driven by parallel evolutionary pressures and intensified global population mobility, effectively transforming the world into a single epidemic zone. One concerning trend is the emergence of MRBP *B. pertussis*, which is widespread in China and, to date, detected only sporadically in Europe. These developments undermine the vaccine-controllability of pertussis and indicate a transition, at this stage, toward a re-emerging infectious disease. This situation underscores the urgent need for widespread integration of molecular genetic surveillance into routine epidemiological monitoring of pertussis, along with the continuous refinement of vaccination strategies and policies based on genomic data.

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ЕВОЛЮЦІЯ БАКТЕРІЇ *BORDETELLA PERTUSSIS*
ПІД ВПЛИВОМ ВАКЦИНАЦІЇ ТА ЇЇ МОЛЕКУЛЯРНО-ГЕНЕТИЧНІ ВЛАСТИВОСТІ

В останні десятиріччя у світі спостерігається тенденція до зростання захворюваності на кашлюк та зміни його епідеміологічних характеристик у бік набуття реемерджентних властивостей. Особливо вираженою ця тенденція є в період після пандемії COVID-19 в Європейському регіоні (87 558 випадків у 2023 р.), зокрема і в Україні (7545 випадків у 2024 р.). Однією з причин такої ситуації вважають впровадження в частині країн світу ацелюлярної вакцини проти кашлюку (аР), за рахунок менш тривалого післявакцинального імунітету та втрати циркулюючими *Bordetella pertussis* певних антигенів під тиском специфічних післявакцинальних антитіл. Однак в Україні натепер для рутинної вакцинації застосовується цільноклітинна вакцина (wP). **Мета роботи.** Узагальнити наукову інформацію щодо біологічних властивостей *B. pertussis,* що циркулюють на різних територіях і сформувалися на тлі застосування вакцин аР та wP. Проаналізовано фактори вірулентності *B. pertussis,* зокрема і ті, що мають антигенні властивості і використовуються у вакцинах аР. Проведено аналіз наукових даних щодо молекулярно-генетичних та антигенних характеристик варіантів *B. pertussis,* що циркулюють у країнах, де використовуються вакцини аР та wP. Зроблено **висновок**, що багаторічна вакцинопрофілактика кашлюку, з одного боку, привела до різкого зниження захворюваності на цю інфекцію, а з іншого боку, обумовила подальшу еволюцію *B. pertussis*, сприяючи зміні або втраті її певних антигенів та подальшій генетичній віддаленості від вакцинних штамів як аР, так і wP. Це дозволило патогену ухилятися від дії специфічного імунітету як на індивідуальному, так і на популяційному рівнях і викликало зростання захворюваності. Вакцини аР у більшій мірі прискорюють такі еволюційні зміни. При цьому розмаїття генетичних варіантів на територіях, де застосовують аР, є більшим, порівняно з територіями, де використовують wP (можуть навіть обмежуватися клональними варіантами). У той же час, спостерігається тенденція до все більшої схожості циркулюючих у світі *B. pertussis.* Це може бути обумовлено як однаковою спрямованістю еволюційних змін, так і інтенсивними популяційними міграційними процесами, що перетворюють Земну кулю на єдину епідемічну зону. Однією з негативних тенденцій є формування макролід-резистентних варіантів *B. pertussis*, що широко спостерігається в Китаї та спорадично зустрічається в Європі. Усе зазначене сприяє втраті кашлюком вакцинокерованості та появі тенденції до переходу на даному етапі до реемерджентних інфекцій. Це потребує широкого впровадження в епідеміологічний нагляд за кашлюком молекулярно-генетичного моніторингу та удосконалення за його результатами стратегії і тактики вакцинопрофілактики.

***Ключові слова**: B. pertussis, молекулярно-генетичні властивості, антигени, ацелюлярна вакцина, цільноклітинна вакцина, вакцинопрофілактика, реемерджентна інфекція.*