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Annual Report of the Swiss National Reference Center for Meningococci, 2024

Address

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1. Introduction

Neisseria meningitidis is a typical benign colonizer of the healty human nasopharynx, but it can also cause invasive meningococcal disease (IMD). Colonized people spread the bacteria to others by respiratory secretions (e.g., saliva droplets) [1]. When the conditions are met in at risk-people, the transmitted bacteria invade the body and cause different types of illnesses. The most commun clinical picture is meningitis and sepsis [2]. Invasive meningococcal infection is an overwhelming disease that is leading to substantial mortality and morbidity [3]. The case fatality rate of *N. meningitidis* is about 7% in high income countries. However, in low income countries, the fatality rate can reach up to 50% [1]. Developmental disorders, and hearing loss remain among the major neurological sequelae observed in the survivors of the disease [2]. Owing to rapid onset of IMD and the related risk of serious morbidity and mortality, accurate and early diagnosis of the disease coupled to the administration of appropriate treatment are major elements of an adequate patient's management [4]. Additionally, prompt identification of close contacts and post-exposure prophylaxis contribute to prevent secondary cases.

The immense majority of *N. meningitidis* strains involved in IMD are encapsulated. The capsule enables the resistance to the humoral immune response and its subsequent dissemination. In contrast, non-capsulated *N. meningitidis* strains are susceptible to opsonization and rarely implicated in invasive infections. However, a few cases of IMD caused by non-capsulated *N. meningitidis* were reported. For instance, a Japanese male taxi driver with a immunoglobulin G4 (IgG4)-related disease developed a bacteremia complicated by a meningitis [5]. The pathogen was a non-capsulated *N. meningitidis.* In Switzerland, together with Dr Nina Lutz,. we reported the first primary meningococcal arthritis caused by a non-encapsulated *N. meningitidis* strain in a previously healthy 52-year-old man [6] .

The increasing antimicrobial resistance of important human pathogenic bacteria remains a key public health concern. Steady increase of multidrug-resistant *Neisseria gonorrhoeae* isolates represent one of the important threats worldwide [7]. In contrast, *N. meningitidis* seems spared of antibiotic resistance. Nevertheless, since the 1980s *N. meningitidis* isolates exhibiting decrease susceptibility to penicillin were reported in different countries [8]. Nowadays, penicillin-resistant *N. meningitidis* strains are widely reported across the world [9]. The important mechanisms related to penicillin resistance are changes in five critical residues of PBP2 (F504L, A510V, I515V, H541N, and I566V) conferred by mutations in the *penA* gene [10]. Penicillin-resistant strains with high minimal

inhibitory concentration (MIC >2 mg/mL) were rarely described. This high penicillin MIC is achieved by chromosomal or plasmid-mediated β-lactamase which is derived from the *Haemophilus influenzae* ROB-1 β-lactamase [11].

N. meningitidis is categorized into 12 defined serogroups, and the major part of invasive meningococcal disease (IMD) cases worldwide are caused by six serogroups: A, B, C, W, X, and Y [12].

Invasive strains of *N. meningitidis* can cause outbreaks and therefore require a continuous surveillance, especially nowadays with the spread of a hypervirulent serogroup W clone in Europe [13]. Also, sporadic cases may occur in any age group and every effort must be undertaken to optimize the prevention, diagnosis and treatment of such infections.

The last decade has witnessed considerable changes in the epidemiology of invasive meningococcal infections in Europe and Switzerland with the increase in the prevalence of Y and W serogroups. Arthritis, pharyngitis, and pneumonia represent some of the atypical clinical manifestations related to these serogroups.

In Switzerland, invasive meningococcal diseases have to be reported to the Swiss Federal Office of Public Health (SFOPH), and corresponding isolates should be referred to the Swiss National Reference Center for Meningococci (CNM, Centre National des Méningocoques; http://www.meningo.ch) at the University Hospital in Geneva.

The CNM provides reference testing of invasive *N. meningitidis* isolates in collaboration with the SFOPH, and currently performs serotyping and molecular typing following protocols recommended by the European Meningococcal Disease Society (EMGM) (http://emgm.eu). Based on a combination of serogroup and molecular typing data, each strain is classified and data are integrated into national (SFOPH) and international epidemiological databases (European Meningococcal Epidemiology in Real Time [EMERT] database; http://emgm.eu/emert) in order to monitor and share information about trends in meningococcal populations. This methodology is evolving towards Next Generation Sequencing (NGS) [14], a method that we used for a selection of cases collected between 2010 and 2016, to determine the clonality of the meningococcal strains of serogroup W finetype (PorA 5,2:FetA 1-1:ST-11). This was executed as a separate subproject supported by the SFOPH (Decision 16.928412). This annual report describes the methods used and results obtained at the CNM during the calendar year 2024.

2. Materials and Methods

The CNM is investigating invasive isolates of *N. meningitidis* as well as native clinical specimens derived from normally sterile body sites.

Isolates are sub-cultured overnight on chocolate agar plates. The identification is confirmed by PCR using the *N. meningitidis*-specific targets *ctrA*, *sodC*, *tauE, metA*, and *shlA*. Serogroups are assessed by PCR as well as by commercial agglutination kits: A, B and C (Pastorex Meningitis, Bio-Rad) and W135, X, Y, Z and Z' (Difco Neisseria Meningitidis Antisera, Becton Dickinson).

Sequence analysis is performed on each isolate in two variable regions of the gene encoding the antigenic outer membrane protein porin A (*porA*-VR1 and *porA*-VR2) and in one variable region of the *fetA* gene (*fetA*-VR) encoding another outer membrane protein exhibiting sequence data which can be useful for tracing clones emerging or circulating in local populations (World Health Organization Manual – Laboratory Methods for the Diagnosis of Meningitis caused by *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*).

In addition, multilocus sequence typing (MLST) is carried out on each isolate according to protocols recommended by the EMGM (http://emgm.eu). This approach is targeting variable regions of seven house-keeping genes (*abcZ*, encoding a putative ABC transporter; *adk*, adenylate kinase; *aroE*, shikimate dehydrogenase; *fumC*, fumurate dehydrogenase; *gdh*, glucose-6-phosphate dehydrogenase; *pdhC*, pyruvate dehydrogenase subunit, and *pgm*, phophoglucomutase). Each isolate is classified according to its multilocus genotype designated as a sequence type (ST), which is the combination of its alleles over the seven genetic loci tested. STs can be further grouped into clonal complexes (CC), which are defined in the *Neisseria* MLST profile database as groups of STs that share at least four of the seven loci in common with a central ST (http://pubmlst.org/neisseria/).

Isolates are then classified based on a combination of serotyping and molecular typing data according to the following scheme:

Serogroup : *porA*-VR1, *porA*-VR2 : *fetA*-VR : MLST (ST or CC).

The antimicrobial susceptibility testing is performed for each isolate using Mueller-Hinton agar + 5% defibrinated horse blood and 20 mg/L β-NAD (MH-F, bioMérieux). Minimum inhibitory concentrations (MICs) are measured for penicillin, ceftriaxone, meropenem, ciprofloxacin, minocycline and rifampicin by E-test strips (AB Biodisk, bioMérieux). The MICs are interpreted according to the current breakpoints recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, www.eucast.org).

In case of no growth of the strain, clinical specimens are analyzed by qPCR to screen for *N. meningitidis* DNA , and if present, we assess the occurrence of the main serogroups by amplifying their corresponding genetic targets. Nucleic acid extraction from clinical specimens such as cerebrospinal fluid and EDTA blood is performed using the MagPurix 12 Nucleic Acid Extraction System (Zinexts Life science; Taiwan). DNA is amplified by real-time PCR to screen for the presence of the *N. meningitidis*-specific targets described above (panel has been completed based on Diene et al, 2016). PCR assays targeting the polysialyltransferase (*siaD*) gene are performed to assign *N. meningitidis*-positive specimens to serogroups B, C and Y/W135; assignment to serogroup A is achieved by qPCR targeting the *sacC* gene. Finally, differentiation between serogroups Y and W135 is asessed by amplification of the *synF* gene (Y) and *synG* gene (W135) [15].

3. Strain collection

The CNM stores all the received invasive meningococcal isolates at -80°C. The collection currently includes more than 500 isolates (between 2009 and 2024). Previous strains were also stored but their recovery by culture cannot be guaranteed (n=1’914 isolates between 1989 and 2009).

4. National and International quality assurance

There is currently no international quality assurance pertaining to meningococci. We are actively scouting whether this service would become available.

5. Epidemiological research

The precision of NGS permitted us to identify several independent monoclonal outbreaks related to *N. meningitidis* W135 that occurred between 2010 and 2016 in Switzerland. Our meta-analyses included samples from other previously published works and allowed establishing connections between Swiss MenWs and other European outbreaks as published recently in the Journal of Infection [16]. This project was made possible through a specific grant from SFOPH (Decision 16.928412).

We have analyzed the molecular epidemiology of *N. meningitidis* W135 (NmW) between 2017 and 2018 in Switzerland. In this period, we reported the circulation of three main NmW lineages: the Hajj-related, South American and ST-9316. While the first two lineages are part of the same clonal complex 11 and were already present in Switzerland, ST-9316 was new and emerged in 2018 in the canton of Vaud.

We highlighted that the distribution of cc11 lineages is quite heterogenous without a precise geographical localization. We identified several outbreaks that occurred in 2017-2018 due to cc11 lineages. In particular, we observed that some of these outbreaks were sub-variants of already circulating strains. Monitoring the current situation by WGS is strongly recommended as the heterogeneity of circulating lineages detected so far can favor the evolution and emergence of new strains.

Acoording to our analyses, the WGS represents the only technique that can allow to capture a detailed epidemiological picture, nation-wide, of a complex species like *Neisseria meningitidis*.

6. Additional meningococcal research

We published recently two papers:

Borrow R, Campbell H, Caugant DA, Cherkaoui A, Claus H *et al.* Global Meningococcal Initiative: Insights on antibiotic resistance, control strategies and advocacy efforts in Western Europe. Journal of Infection 89 (2024) 106335 / https://doi.org/10.1016/j.jinf.2024.106335

Lutz N, Lazarevic V, Gaïa N, Cherkaoui A, and Schrenzel J. Primary meningococcal arthritis by a nonencapsulated *Neisseria meningitidis* strain. *Clinical Microbiology and Infection 2025* / https://doi.org/10.1016/j.cmi.2025.02.005

7. Advisory service and Networking

7.1 Advisory service

Molecular testing:

We systematically conduct molecular assays to define the serogroups using isolates or directly from clinical specimens when the bacterial growth is not possible (or suspicion thereof). As mentioned above, it is likely that the true incidence of invasive *N. meningitidis* infection is missed by rapid empiric therapy (precluding successful cultivation), nor to mention the new clinical presentations related to W135 such as pneumoniae (typically undetected and not referred to the CNM unless presenting with a bacteraemia and thus fulfilling the current definition of invasive infection). Our current molecular approach covers the most frequent serotypes and a result can usually be communicated to the clinicians.

7.2 Networking

We have established contact with the Italian reference center for meningococci to further analyze our peculiar W135 epidemics, in conjunction with their national epidemiology.

7.3 Website

The dedicated website (www.meningo.ch) was fully rebuilt in 2018, and is available in French, German, Italian and English. We are currently updating it to better display the information.

8. Results

8.1. Phenotypic and molecular characterization

During the calendar year 2024, the CNM has received a total of 26 invasive isolates of *N. meningitidis*. These strains were isolated from blood cultures (n=21) and cerebrospinal fluid (n=5). In addition, a qPCR assays was performed on one CSF because there was no growth of the strain (Figure-1). The Figure-2 depicts the number of *N. meningitidis* strains isolated in 2024 according to gender and serogroups.

Since 2014, the number of invasive meningococci isolated was increasing (Figure 3). However, in 2021 and 2022, the number of invasive *N. menigitidis* isolates was very low compared to previous years. Similar to 2020, this downward trend already observed in 2019 was deeply magnified by the sanitary situation linked to Sars-CoV-2. Invasive meningococcal disease cases in the Switzerland have increased moderately since 2021. We have not yet reached the pre-pandemic levels. In 2024, 35 confirmed IMD cases were reported in Switzerland, of which we received 26 isolates and one CSF specimen (77%, 27/35).

The last decade has however witnessed considerable changes in the epidemiology of invasive meningococcal infections in Switzerland. In 2024 serogroup Y was the most frequently invasive serogroup (14/27; 52%), followed by serogroups B (8/27; 30%), W (3/27; 11%), and C (2/27; 7%) (Figure 4 and Figure-5).

Figure-6 depicts the number of *N. meningitidis* strains collected in 2024 and classified by serogroups and age groups.

Figure-7 shows the distribution of serogroups by geographical regions in 2024. Only two strains were referred from the Italian speaking region.

Molecular characterization using MLST (Table -1a, -1b, -1c and -1d, and Figure 8) revealed that ST23 and ST23 complex was the most prevalent sequence type among the 14 serogroup Y strains analyzed in 2024 (9/14, 62%) followed by ST1655 (4/14, 29%).

8.2. Antimicrobial Susceptibility Testing

Table-2 depicts the antimicrobial susceptibility profiles and the MICs ranges by drugs, with the MIC_{50} and MIC_{90} of the 26 invasive *N. meningitidis* strains referred to the Swiss National Reference Center for meningococci in 2024. Applying EUCAST breakpoints (v12; 2024), all invasive *N. meningitidis* strains tested were susceptible to ceftriaxone, meropenem, ciprofloxacin, minocycline and rifampicin.

However, 2 strains (8%, 2/26) exhibited low resistance levels to penicillin (MIC = 0.38 mg/l). The molecular analysis of these strains showed the presence of mutations in the five critical residues of PBP2 (F504L, A510V, I515V, H541N, and I566V).

Summary of key observations

- Invasive meningococcal disease cases in the Switzerland have increased moderately since 2021. We have not yet reached the pre-pandemic levels. In 2024, serogroup Y was the most frequent invasive serogroup (14/27; 52%), followed by serogroups B (8/27; 30%), W (3/27; 11%), and C (2/27; 7%)
- ST23 was the most prevalent sequence type among the 14 serogroup Y strains analyzed in 2024.
- The ciprofloxacin- and high levels penicillin-resistant strains identified in 2023 were not observed in 2024.
- A non-encapsulated *N. meningitidis* strain was reported to the Swiss National Reference Center for meningococci by Dr Nina Lutz, sequenced and analyzed, confirming this rare instance in a non-immunocompromised individual.

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9. Discussion

The incidence of IMD in 2024 was 0.39 for 100'000, which corresponds to 35 cases reported to the SFOPH. We have not reached the pre-pandemic levels. The incidence in 2023 has exceeded the level recorded in 2020 (0.38 *versus* 0.23 in 2020), and has even doubled when compared to 2022 (0.38 *versus* 0.19 in 2022).

The proportion of serogroup Y among the invasive strains in 2024 has increased considerably compared to 2022; 52% (14/27) versus 17% (2/12), and exceeded the peak observed in 2018 (12 IMD cauded by serogroup Y).

The *N. meningitidis* ROB-1 β-lactamase producer, serogroup Y, isolated in 2023 was not observed among the strains isolated in 2024, which is reassuring. The same held true for ciprofloxacin-resistant *N. meningitidis* strain, serogroup B, identified last year in Bern from the bloodstream of a 25-year-old man. However, the monitoring and the follow-up of the ciprofloxacin-and penicillin-resistant *N. meningitidis* strains among the invasive and the colonizer strains should be enforced and pursued.

Across Western Europe the incidence of IMD is still low (Table-2). Men B remains the foremost serogroup. Nevertheless in the last few years, MenY and MenW cases have emerged in some EU countries like Switzerland. Very recently, an outbreak of Men B was reported in Rennes, France, prompting for large scale immunization after NGS confirmed a clonal outbreak.

All the 26 Nmen strains isolated in 2024 were submitted to Public databases for molecular typing and microbial genome diversity (https://pubmlst.org/organisms/neisseria-spp/submissions).

Table-2

Source : Borrow *et al.* 2025 / https://doi.org/10.1016/j.jinf.2024.106335

Country	Surveillance system (Y/N)	Epidemiology
Austria	Y	– Incidence (2023): 0.18 cases per 100,000 people – Number of cases (2023): 16 cases – Serogroups (2023): MenB (11/16), MenY (2/16), MenC (1/16)
Belgium	Y	– Incidence (2023): 0.71 cases per 100,000 people – Number of cases (2023): 83 cases – CFR (2023): 3.6% – Serogroups (2023): MenB (42.2%), MenW (22.9%), MenY (28.9%)
England	Y	– Number of cases (2021–2022): 205 cases – Serogroups (2021–2022): MenB (87%), MenW (6%), MenY (2%)
Finland	Y	– Incidence (2023): 0.2 cases per 100,000 people – Number of cases (2023): 10 cases – Serogroups (2023): MenB (60%), MenY (10%), non-groupable (20%), Not known (10%)
France	Y	– Incidence (2023): 0.82 cases per 100,000 people – Serogroups (2023): MenB (44%), MenW (29%), MenY (24%), MenC (1%)
Germany	Y	– Incidence (2023): 0.3 cases per 100,000 people – Serogroups (2023): MenB (40–50%), MenY (40–50%)
Greece	Y	– Incidence (2023): 0.2 cases per 100,000 people – Number of cases (2023): 21 cases CFR (2023): 5.26%
Italy	Y	– Incidence (2022): 0.1 cases per 100,000 people – Number of lab-confirmed cases (2022): 57 cases – Serogroups: MenB (80%) in 2022
Netherlands	Y	– Number of cases (2023): 120 cases – Serogroups (2023): MenB predominant serogroup (87%)
Norway	Y	– Number of cases (2023): 16 cases; incidence 0.29 per 100,000 people – Serogroups (2023): MenB (7/16), MenY (5/16), MenW (2/16), MenA (1/16), MenC (1/16)
Portugal	Y	– Incidence rate (2023): 0.27 cases per 100,000 people – Highest incidence rate in children under 12 months (14.6), with a notable decrease in the 1–4 years age group (3.6) and adults ≥45 years (0.25) – Serogroups (2012–2023): MenB (65%), MenY (9.1%), MenW (6.1%) and MenC (5%)
Spain	Y	– Incidence (2022/2023): 0.45 cases per 100,000 people – Serogroups (2023): MemB (54.9%), MenC /1.7%), MenW (20.9%), MenY (15.1%)
Sweden	Y	– Number of cases (2023): 33 cases, incidence of 0.31 cases per 100,000 people, CFR 9.1% – Most cases in the age of 15–24 (n = 12) – Equal distribution of cases among gender – Serogroups (2023): MenB (29%), MenY (23%), MenW (23%), MenC (6%), MenX (3%)
Switzerland	Y	– Number of cases (2023): 34 cases – Incidence (2019 - 2023): 0.51, 0.23, 0.09, 0.19, and 0.38 cases per 100,000 people in each year, respectively. – Serogroups (2023): MenY (42%), MenB (35%), and MenW (23%)

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Figures

Figure 1. Number of *N. meningitidis* identified in 2024 according to the age of the patients and the specimen types.

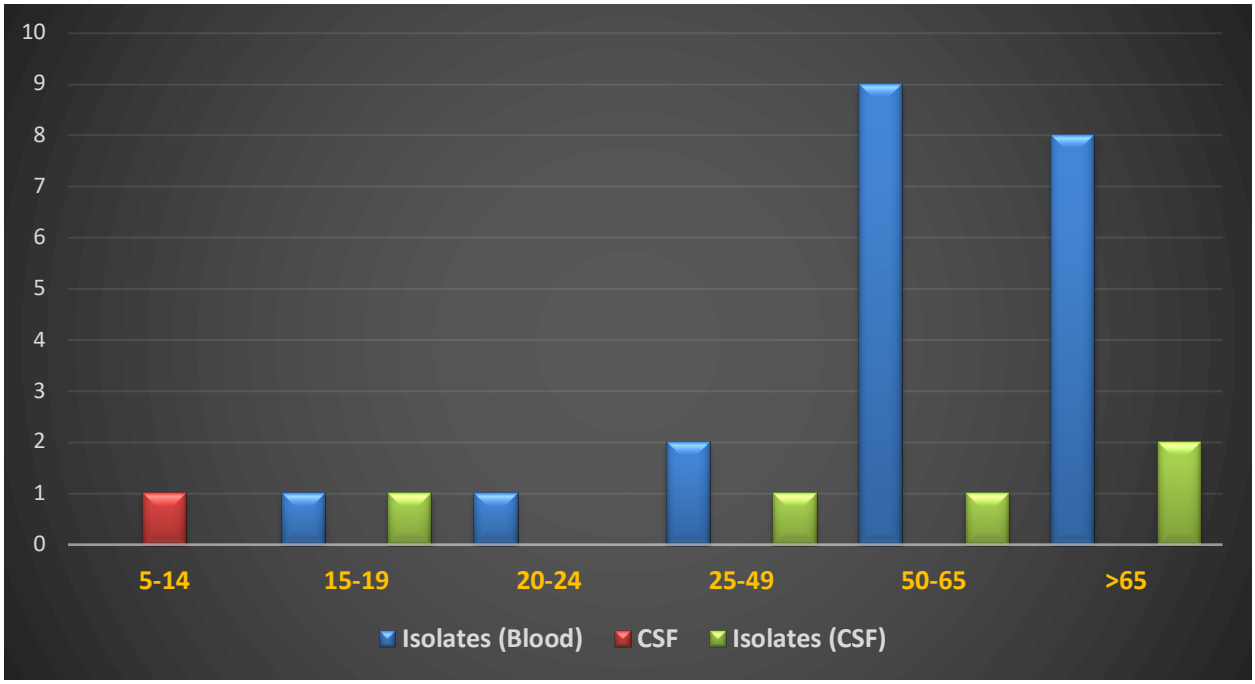

Figure 2. Number of *N. meningitidis* strains isolated in 2024 according to gender and serogroups.

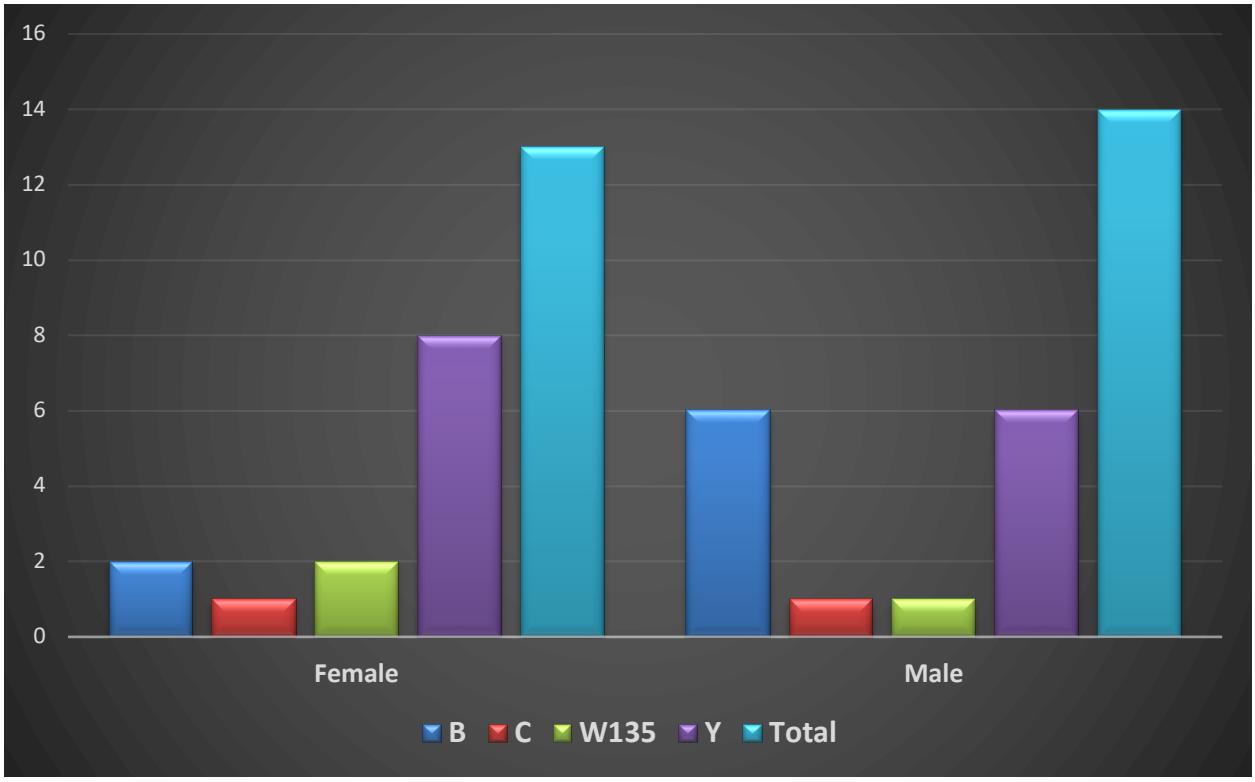

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Figure 3. Annual number of cases of invasive meningococcal diseases reported to the Swiss Federal Office of Public Health (SFOPH) and number of *N. meningitidis* strains referred to the Swiss National Reference Center for Meningococci (SNRCM) from 2009 to 2024

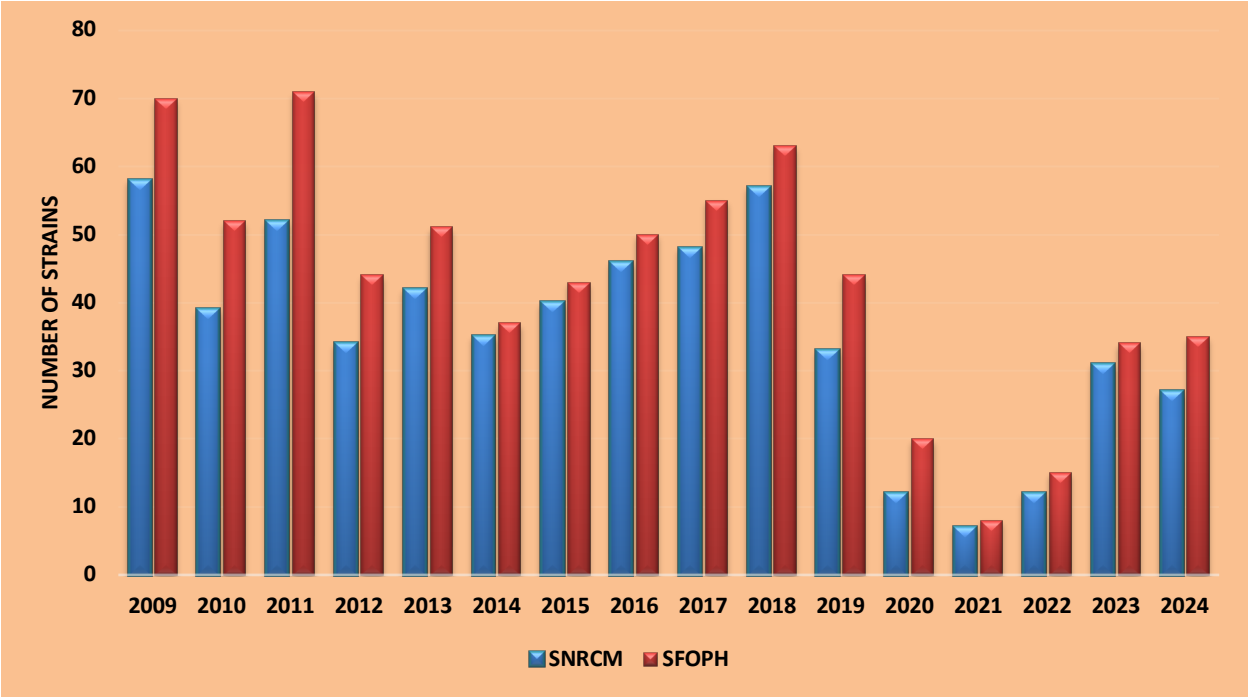

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Figure 4. Serogroups distribution in 2024 (n=27)

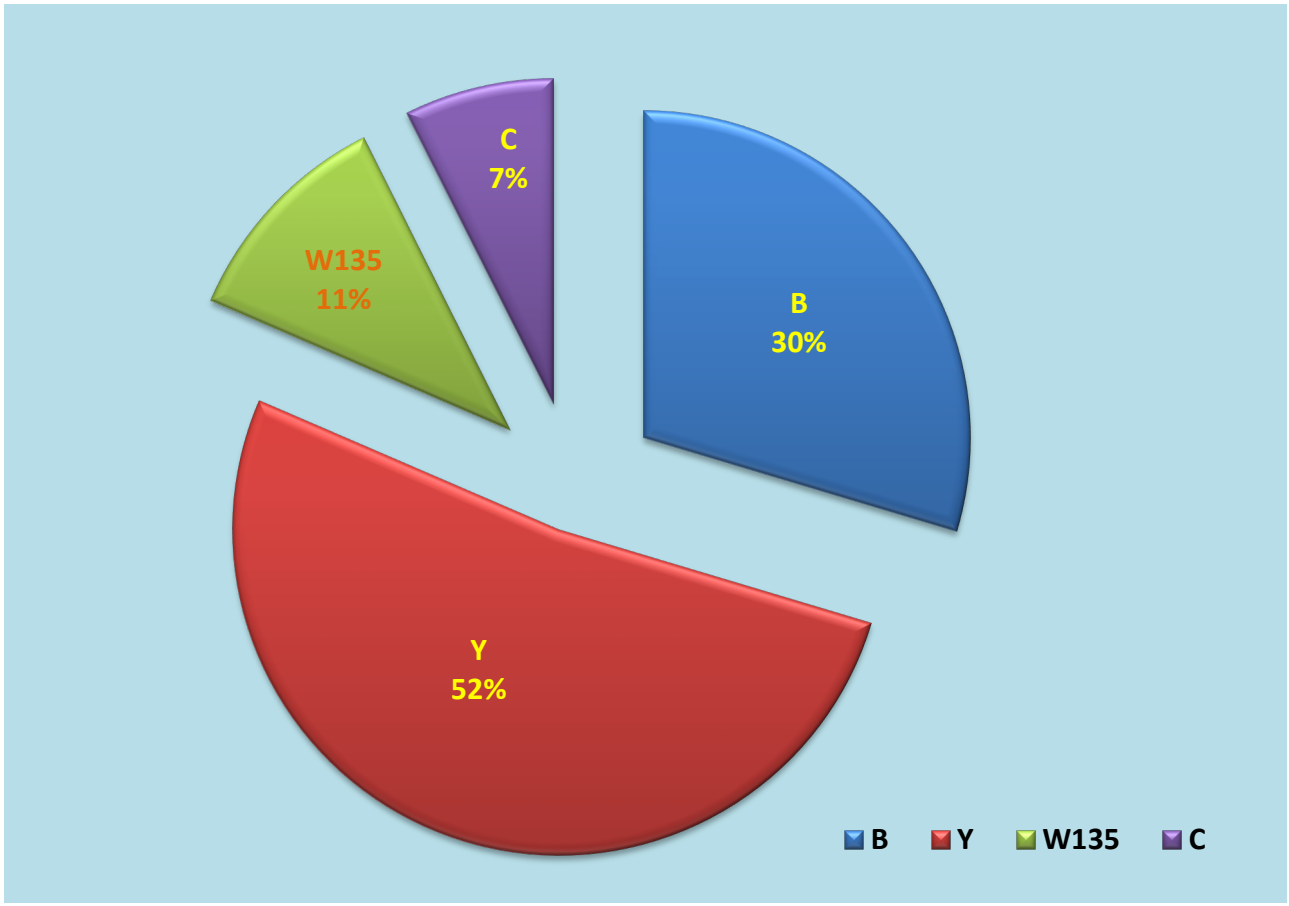

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Figure 5. Annual number of strains representing the main serogroups B, C, X, Y and W135 of invasive *N. meningitidis* as determined at the Swiss National Reference Center for meningococci from 2009 to 2024

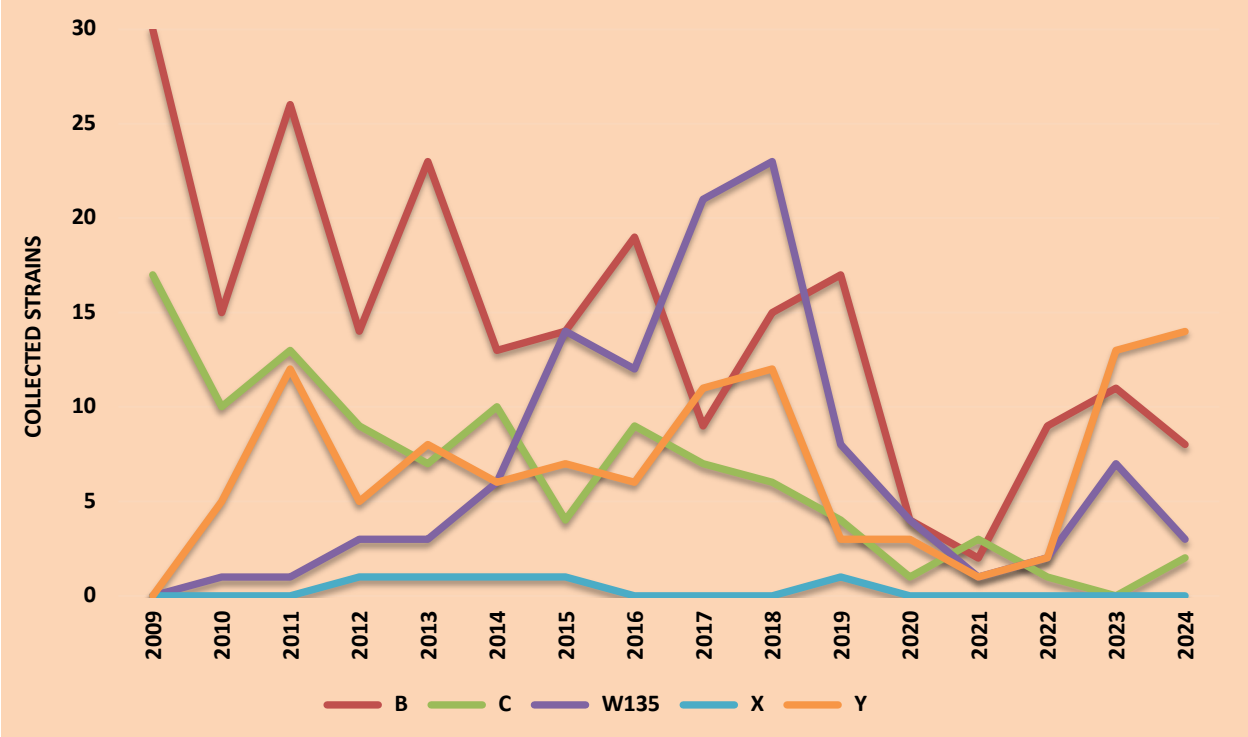

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Figure 6. Number of *N. meningitidis* strains isolated in 2024 according to age and serogroups.

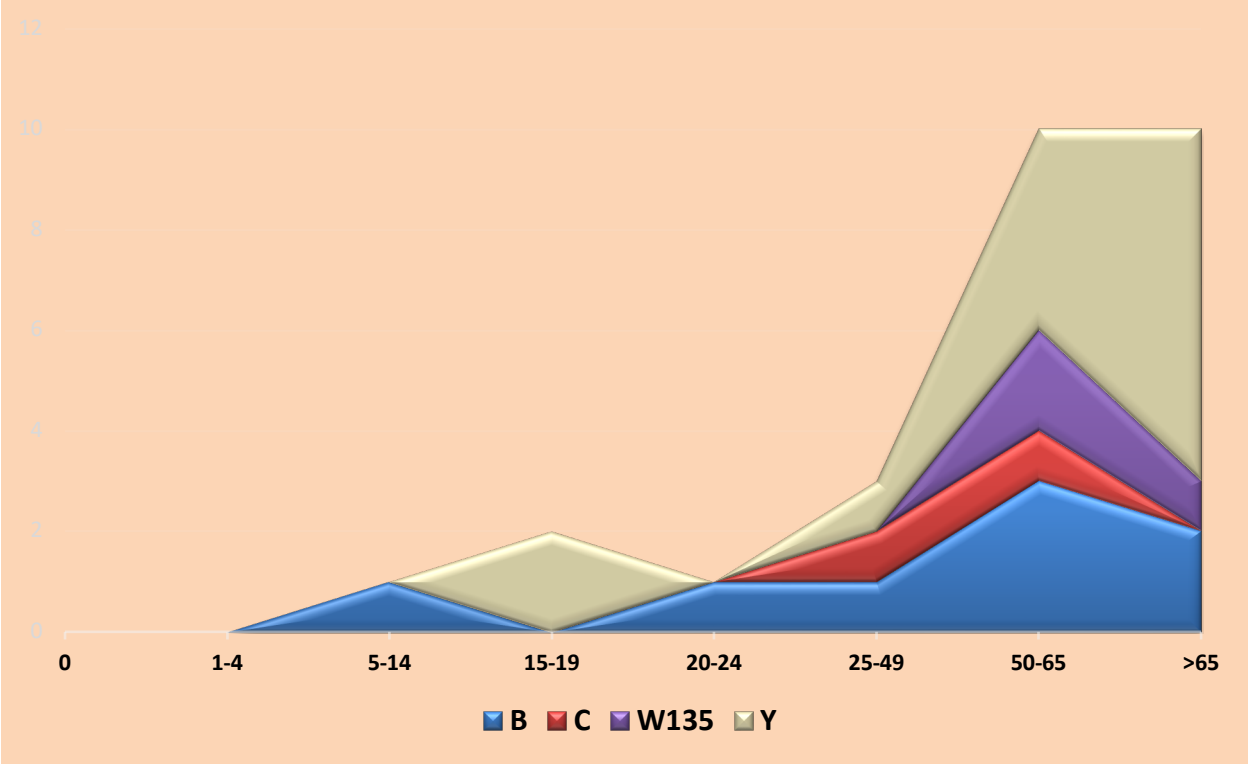

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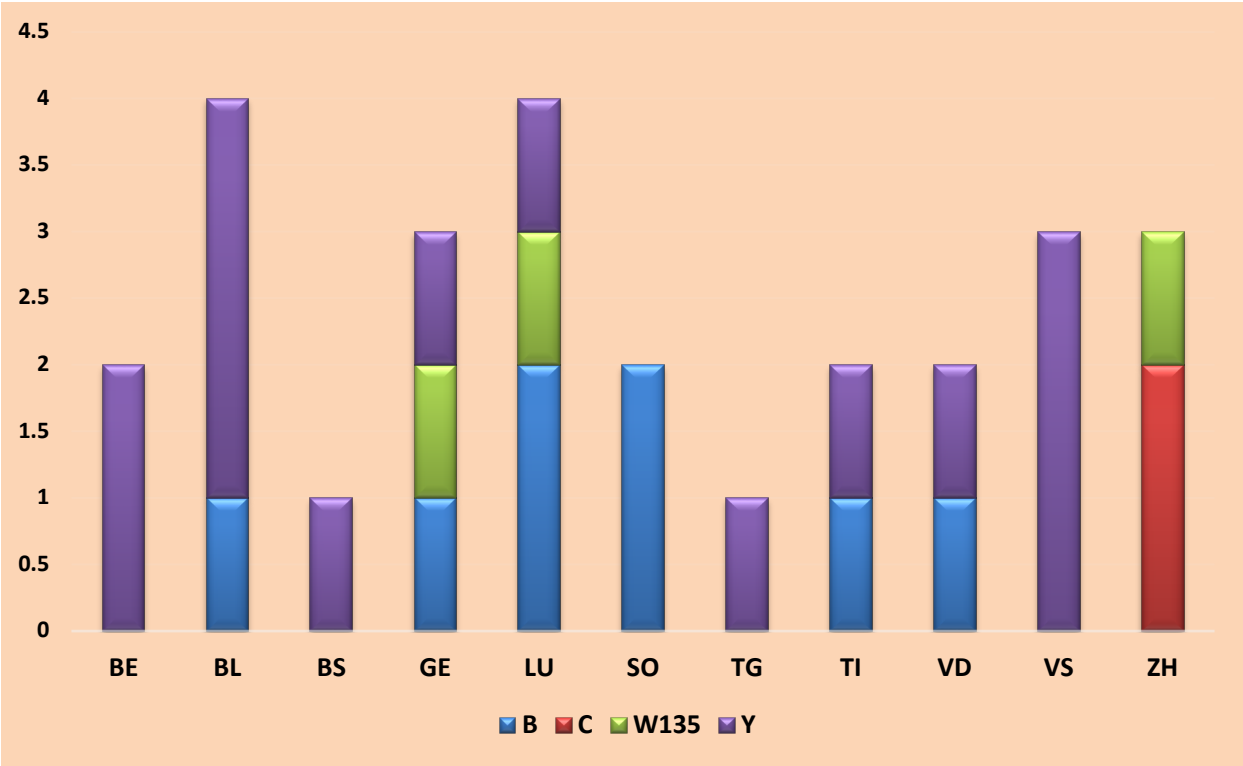
Figure 7. Distribution of serogroups by geographical regions in 2024



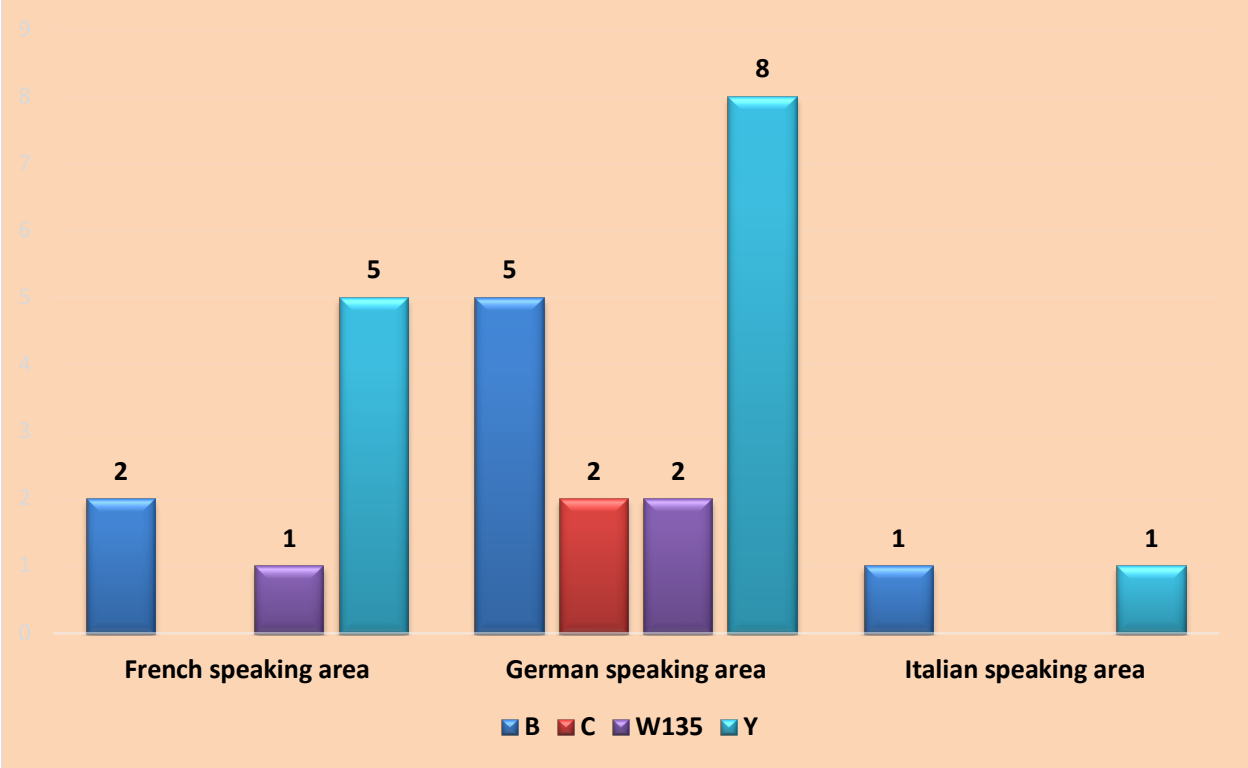


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Figure 8. Distribution of sequence types in 2024

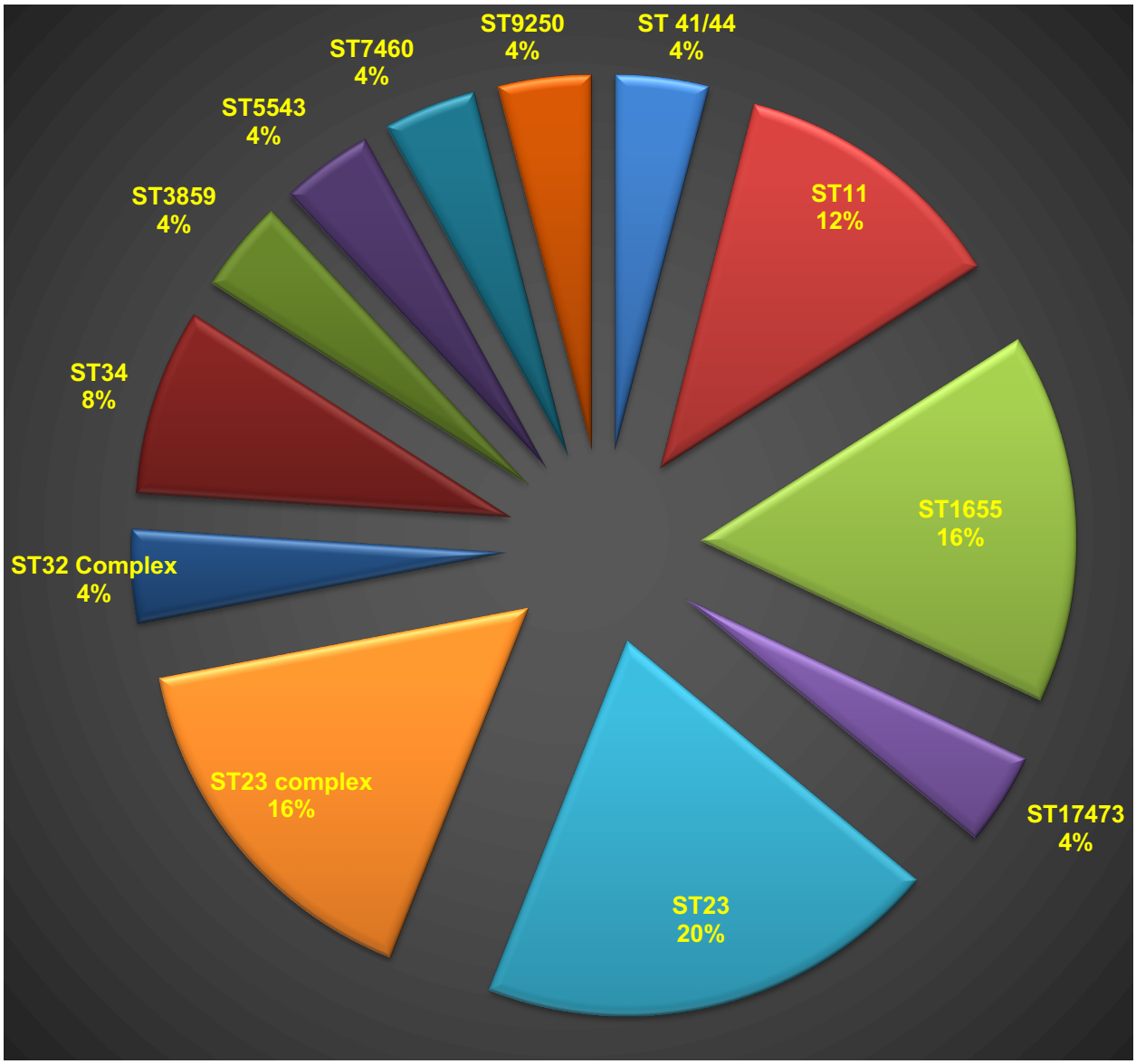

Table 1. Synopsis of MLST profiles and serogroups of invasive *N. meningitidis* strains referred to the Swiss National Reference Center for meningococci in 2024

[a] *N. meningitidis* isolated from	Canton	Serogroup	Sequence types (STs)
Blood culture	TG	**Y**	**ST23 complex**
Cerebrospinal fluid	VS	**Y**	**ST23 complex**
Blood culture	VS	**Y**	**ST23 complex**
Blood culture	BS	**Y**	**ST23 complex**
Blood culture	VS	**Y**	**ST23**
Blood culture	VD	**Y**	**ST23**
Blood culture	LU	**Y**	**ST23**
Cerebrospinal fluid	GE	**Y**	**ST23**
Blood culture	BE	**Y**	**ST23**
Blood culture	BL	**Y**	**ST1655**
Blood culture	BL	**Y**	**ST1655**
Blood culture	BL	**Y**	**ST1655**
Blood culture	TI	**Y**	**ST1655**
Cerebrospinal fluid	BE	**Y**	**ND**

[b] *N. meningitidis* isolated from	Canton	Serogroup	Sequence types (STs)
Blood culture	SO	**B**	**ST34**
Blood culture	SO	**B**	**ST34**
Cerebrospinal fluid	TI	**B**	**ST 41/44**
Blood culture	TI	**B**	**ST 41/44**
Blood culture	LU	**B**	**ST5543**
Blood culture	LU	**B**	**ST7460**
Blood culture	BL	**B**	**ST9250**
Cerebrospinal fluid	VD	**B**	**ND**
Direct sample analysis (no growth)			
Cerebrospinal fluid	GE	**B**	**ST32 Complex**

[c] *N. meningitidis* isolated from	Canton	Serogroup	Sequence types (STs)
Blood culture	ZH	**C**	**ST11**
Cerebrospinal fluid	ZH	**C**	**ST17473**

	Canton	Serogroup	Sequence types (STs)

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[d] *N. meningitidis* isolated from			
Blood culture	LU	**W135**	**ST11**
Blood culture	ZH	**W135**	**ST11**
Blood culture	GE	**W135**	**ST3859**

Table 2. Antimicrobial susceptibility testing (EUCAST breakpoints) of the 26 invasive *N. meningitidis* strains referred to the Swiss National Reference Center for meningococci in 2024

Drugs	Range	Minimum inhibitory concentration (MIC)		Breakpoint susceptible (≤ µg/ml)	% of strains considered susceptible
		MIC50	MIC90		
Penicillin	0,012-0,38	0.094	0.25	0.25	71
Ceftriaxone	0,002-0,016	0.002	0.002	0.12	100
Meropenem	0,003-0,08	0.012	0.047	0.25	100
Ciprofloxacin	0,002-0,006	0.003	0.006	0.016	96.8
Minocycline	0,064-0,5	0.19	0.5	1	96.8
Rifampicin	0,002-0,047	0.012	0.032	0.25	100

Red: increase (resistance) vs 2021
Green: decrease (resistance) vs 2021
Black, identical to 2023