



REFERENCE GRID

MILESTONE 6.1



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Annex 2: description of extraction fields to fill in the first grid (word file).

Annex 3: second grid – grey literature used to extract data from international organisations (excel file).



Introduction

Vaccinations are one of the most beneficial public health interventions.

The general objective of the IMMUNION Work Package (WP) 6 is to create awareness and empower target populations on the benefits of vaccine uptake for individual and public health.

This milestone refers to the first specific objective of WP6, that is, to understand the dynamics preventing access to vaccines to improve uptake in specific target populations.

The starting point to reach this specific objective was the collection and subsequent analysis of existing evidence regarding determinants of vaccine hesitancy in general and during health emergencies (e.g., the COVID-19 pandemic).

The design and use of *two ad hoc grids* was paramount to collect such data. The construction of the grids required careful analysis of existing models and attentive consideration of evidenced-based literature as well as grey literature on vaccine hesitancy determinants. A special focus on grey literature from international organisations is also provided. As such, the first grid focuses on peer-reviewed articles, and the second on grey literature.

Four partner countries participated in this collaborative effort (Italy, Latvia, Romania and Greece), although all countries can use the grid to investigate national-level scenarios.

In terms of next steps, this exercise will allow progress towards achieving WP6's second specific objective, that is, to improve access and encourage the use of reliable and accurate information about vaccination to increase confidence and uptake in specific target populations. WP6 partners will make use of the information in the grid to build the national toolboxes of community engagement and communication tools on vaccination (task 6.2). In addition, the milestone will also provide valuable information for WP5 (developing trainings), WP4 (communication and education materials) and WP2 (communication activities).

This document includes the following:

- 1) a description of the drafting process of the two grids that led to the final version agreed upon by all participating partners, used in order to extract data from literature (methodology section);
- 2) an overview of the main results achieved from the implementation of the grids (results section);
- 3) final considerations.



Methods

First grid (peer-reviewed articles)

To structure a reference grid, we followed a stepwise approach. Initially, we performed a thematic literature search to collect, critically appraise and compare theoretical frameworks, conceptual models and matrixes exploring vaccine hesitancy determinants.

We adopted a modified Delphi technique, whereby several meetings were held within the ISS team in search of a consensus strategy in terms of research priorities and applicability to the current milestone. After an initial phase of internal consultations within the ISS team, the decision-making process was shared with all the WP6 international partners.

The prototype reference grid was mainly informed by a much-cited peer-reviewed article listing key vaccine hesitancy determinants (MacDonald, 2015) and a prominent technical report authored by the European Center for Disease Control and Prevention (ECDC, 2016).

We conceived a flexible strategy, with the perspective of a possible milestone update. We expected novel and hitherto unexplored factors for vaccine hesitancy to emerge during the grid compilation as causally linked or fuelled by the current COVID-19 pandemic. Furthermore, the pandemic has arguably determined a radical paradigm shift in public attitudes toward vaccines and vaccinations.

The draft grid was discussed among partners and received formal approval prior to starting the cooperative work. Only articles in English were eligible for the grid, in order for the lead partner (ISS) to be able to have full control of reported results.

The complete search strategy is reported below.



L1	1186 S VACCINE HESITANCY/CT
L2	18097 S VACCIN?(5A)(HESITANC? OR HESITANT OR HESITAT? OR BEHAVIOR? OR BEHAVIOUR? OR ATTITUDE?)/TI,AB
L3	23907 S VACCIN?(5A)(ACCEPT? OR WILLINGNESS OR COMPLIANCE? OR COMPLACENCY OR COMPLIANT OR CONFIDENCE? OR CONFIDENT)/TI,AB
L4	1187 S VACCINATION REFUSAL/CT
L5	6245 S VACCIN?(5A)(REFUS? OR REJECT? OR RELUCTANCE? OR RELUCTANT)/TI,AB
L6	17540 S VACCIN?(5A)(ANXIET? OR FEAR? OR DOUBT? OR CONTROVERS? OR DILEMMA? OR RUMOR? OR RUMOUR? OR INTENT? OR DELAY?)/TI,AB
L7	16192 S VACCIN?(5A)(AWARENESS OR BELIEF? OR PERCEPTION? OR PERCEIV? OR CRITICIS? OR SCEPTIC? OR DROPOUT? OR EXEMPTION?)/TI,AB
L8	4208 S VACCIN?(5A)(TRUST? OR DISTRUST? OR MISTRUST? OR MISCONCEPTION? OR MISCONCEIV? OR MISINFORM? OR DISINFORM? OR OPPOSITION OR OBJECTOR?)/TI,AB
L9	61154 S L1-L8
L10	1101526 S DETERMINANT?/CT,TI,AB
L11	305267 S GREECE/CT OR ITALY+NT/CT OR LATVIA/CT OR ROMANIA/CT
L12	533760 S (GREECE OR ITALY OR LATVIA OR ROMANIA)/TI,AB
L13	911521 S EUROPEAN UNION/CT,TI,AB OR EUROPE/CT,TI,AB
L14	24004 S EUROPEAN(1W)(COMMUNITY OR AREA)/TI,AB
L15	122319 S EUROPEAN COUNTR?/TI,AB
L16	114 S EUROPEAN COMMON MARKET/TI,AB
L17	1617315 S L11-L16
L18	270 S L9 AND L10 AND L17
L19	268 S L18 AND (ENGLISH OR ITALIAN)/LA
L20	253 S L19 AND (2010-2021)/PY
L21	95 DUP REM L20 (158 DUPLICATES REMOVED)

Figure 1. Search strategy adopted

Even though our review was non-systematic, we followed the PRISMA 2020 guidelines for the selection process. The initial search yielded 95 scholarly articles after duplicate removal. A first title-and-abstract screening restricted the selection to 89 records.

As the peer-reviewed search was ongoing, all participating partners were invited to include additional articles in their local languages. These articles were not included in the final grid due to the eligibility criteria, but they help local partners to gain a better understanding of the situation in their national contexts, and will feed into further WP6 work.

The customized Excel spreadsheet (First grid) is featured in Annex 1. Annex 2 provides an explanatory addendum to Annex 1.

Second grid (grey literature)

In parallel to the reference grid design, we searched the literature to collect meaningful records pertaining to vaccine hesitancy determinants in the four countries of interest (Italy, Romania, Greece, Latvia).

We searched the following electronic databases: Medline, Embase, Biosis, Scisearch, Esbiobase. The search strategy was identical across databases. Relevant keywords and index terms were pooled and connected with Boolean operators (OR, AND).

We selected articles published in English and Italian between January 1, 2010, and July 31, 2021.

We considered relevant grey literature produced by national and international organizations - including, but not limited to, the following websites: the World Health Organization (WHO), the ECDC, the European Commission (EC), the Italian Ministry of Health and the Italian National Institute of Health. These records inherently lack original data, and their value lies in the strength of the overall body of advice to policymakers and technical support to public health officials. Therefore, we decided to use a simplified grid to extract data from the grey literature (Annex 3).

The final number of selected records (peer-reviewed and grey literature) was 57, as shown by the PRISMA-style flow diagram below.



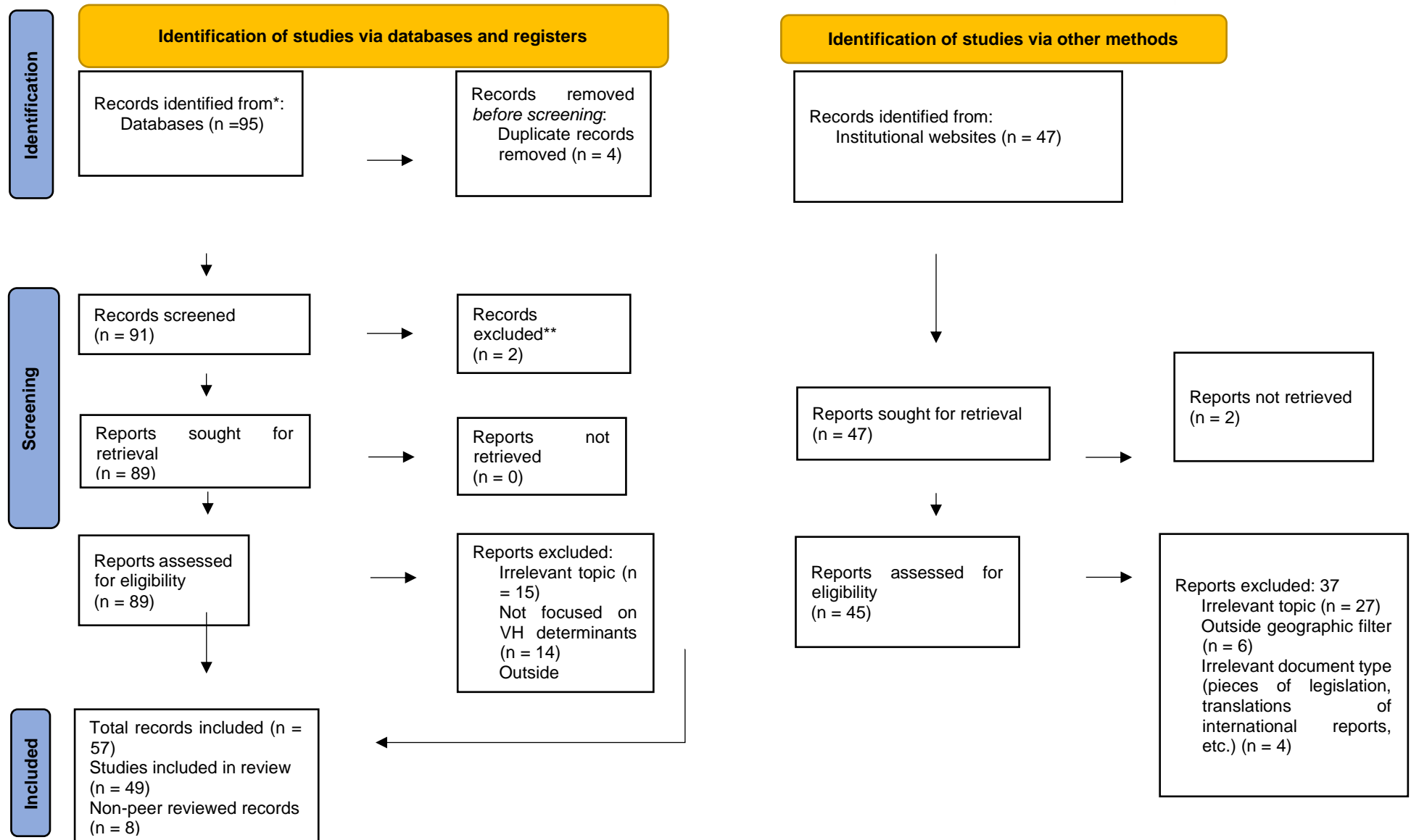


Figure 2. PRISMA-style flow diagram showing the selection process.

Results

Main features of the records included

Overall, the combined literature search resulted in 57 records. Of those, 49 (86%) were peer-reviewed articles, while the remaining 8 (14%) were grey literature items.

- **Peer-reviewed articles (see Annex 1)**

Italy accounted for a majority of the surveyed scholarly articles (29/49, 59%). Almost a third of the records was set in Greece (8/49, 16%) or Romania (6/49, 12%). A total of 6 articles (6/49, 12%) were multi-country based, predominantly in Greece, Italy and Romania combined (3/6, 50%). Articles from Latvia were uniquely in Latvian, and it was therefore not possible to evaluate them and include them in the grid. A summary of these articles has been included as Appendix 1 of this document.

While publication years spanned from 2010 to 2021, most retrieved articles and reports were published after 2019 (30/49, 61%). Indeed, true study periods, as assessed by the full-text screening performed, dated back some studies as early as 2006, indicating a potential publication bias for records assessing vaccine hesitancy determinants, and confirming its relative novelty as a research topic.

An overwhelming majority of peer-reviewed articles were cross-sectional studies (42/49, 86%). Literature reviews and retrospective cohort studies accounted for five studies, combined (5/49, 10%).

Across studies, there was considerable heterogeneity in the investigated population. This finding undermines the external validity of the current report's findings. Only about one-fifth of the articles dealt with the general population (11/49, 22%), while more than a third (17/49, 35%) explored vaccine hesitancy determinants within the largely defined health workforce (medical doctors, other health and care professionals, nursing and medical students, etc.). Among the other investigated subpopulations were parents/guardians of underage children, young adults, migrants and refugees, pregnant women, and adults with medical comorbidities. For cross-sectional studies, the accrued sample sizes were modest, often including less than 1000 subjects, with a majority of female respondents and an approximate age of 20-50 years old.

The studies mainly report information on the following vaccinations: influenza (14/49, 29%), early childhood vaccines in general (10/49, 20%), HPV vaccine (9/49, 18%), all vaccines generically (8/49, 16%), COVID-19 vaccine (7/49, 14%), recommended vaccines for the health workforce (3/49, 6%), measles (1/49, 2%) and varicella (1/49, 2%) vaccines.¹

A majority of articles (28/49, 57%) predominantly explored knowledge, attitudes and practices, as well as intentions and uptake/coverage, while the rest (21/49, 43%), dealt primarily with determinants of vaccine hesitancy or vaccine refusal, as well as delayed, missed or incomplete vaccinations. There was also overlap between these two objectives. Questionnaires and surveys, often customized by the authors, were the preferred tool for assessing both outcomes, whereas public registries or immunization databases were largely used to objectively quantify vaccination uptake and coverage. Only a few studies used validated items, mainly to assess vaccine hesitancy. Among the validated instruments used were the Parental Attitudes about Childhood Vaccine Survey (PACV), the Vaccine Hesitancy Scale and others.

¹ Totals do not add up to 100%, as some articles deal with more than one vaccine.



Globally, the results confirm that all three vaccine hesitancy categories (1) contextual, 2) individual and group, and 3) vaccine/vaccination-specific influences) influence behavioural decisions to accept, delay or reject some or all vaccines.

- ***Grey literature items (see Annex 3)***

The reports analysed by using the simplified grid (second grid, Annex 3) were authored or commissioned from prominent international organisations, such as the ECDC (4 documents), the EC (3 items), and the WHO (1 report). They provide meaningful insights on current and prospective strategies to tackle vaccine hesitancy, in line with evidence found in the examined scientific literature. Content analysis revealed that vaccine confidence, public trust and online/offline misinformation determinants and mechanisms were among the most recalled themes. The two most recently published reports deal with COVID-19 vaccination. All the reports are addressed to technical targets, even though two of them issued by the EC are aimed at the general population. Country-specific data are present in five out of eight reports, with the following distribution: Romania (5), Italy (4), Greece (3), and Latvia (2). The search of grey literature helped to further understand the picture on vaccine hesitancy in the countries of interest and some highlights can be outlined as follows.

Country specific considerations identified in both peer-review articles and grey literature

- ***Greece***

Under-vaccinated populations identified in the literature include vulnerable groups and minorities, such as Roma populations; migrants/refugees; single and/or young mothers; unemployed parents; poor families; families with many children. In 4 studies, health care professionals' attitudes towards vaccination were investigated. Health professionals seem to be more worried about certain vaccines and less worried about others. Intention to refuse vaccination, mainly for influenza, was due to concerns about safety, inadequate information, not feeling at risk. Studies regarding COVID-19 reveal that more than half of the population are positive towards vaccination, while health care professionals' hesitation is related to inadequate information (74.9%) and concerns about vaccine safety (36.2%). Accordingly, parents seem to be more hesitant towards new vaccines compared to those in the national immunisation schedules, and also tend to delay booster doses. The majority of Greek parents receive vaccine information by their primary care paediatrician (90.8%).

- ***Italy***

In 2018, vaccine confidence levels were quite high both among the population and general practitioners because of a good level of trust in their safety and efficacy. However, nine studies on social media monitoring methods and interventions relating to vaccine hesitancy detected more adverse attitudes to vaccination than favourable positions. On COVID-19, nearly three out of four persons referred to be in favour of getting a vaccine, with the main reason being to help end the pandemic (70%). Opposition among the general population is mainly due to believing that the COVID-19 vaccine was insufficiently tested.

- ***Latvia***

Articles from Latvia were exclusively in Latvian, therefore it was not possible to evaluate them and include them in the grid; they are included as Appendix 1. Studies regarding COVID-19 vaccination reveal



that the main reasons for hesitancy are considerations that the offered vaccines are insufficiently tested (63%), that it is not known how long vaccines will protect against COVID-19 and whether they will be effective against the new strains (60%) and that people want to see how the vaccine works (what are the side effects, etc.) (53%). Conspiracy theories are more prevalent amongst women, respondents living outside Riga who are divorced, unemployed and who have primary or secondary education. Regarding other vaccines, respondents believe that there are other ways of avoiding the disease; vaccination may cause complications and be harmful, and the probability of falling ill is low. The main source of information for parents about vaccination issues are medical specialists, but 17.8% of GPs consider that they have insufficient or outdated knowledge on vaccination.

- **Romania**

The role played by health professionals is highly acknowledged as they are among the most trusted figures and, therefore, in a position to positively address vaccine compliance and uptake in the general population, or to develop and implement communication strategies that would help to reduce the fear of side effects. Healthcare students represent another professional group that can be crucial in spreading essential, scientifically sound information to the public, even more for their attitude on innovative and creative communication through social media and user-friendly tools, above all in having a dialogue with young people. Recent monitoring indicators on vaccination coverage or online misinformation relating to vaccination for vaccine-preventable-diseases focus on measles (in combination with mumps and rubella), influenza, HPV and COVID-19. This last has renewed the overall necessity for implementing the country plan to prevent and respond to epidemic outbreaks, and strengthen the immunisation system overall.



Final considerations

The two grids are useful tools to collect data and provide a better understanding of hesitancy determinants and national scenarios. The recommendations provided by international organisations proved very useful to acquire a full picture and updated information.

A few considerations arise from this exercise. The first reflection concerns the data provided by Latvia (one of the participating countries in this exercise), which was mostly in Latvian. We recommend encouraging all European countries to publish in an international language, in order to be able to disseminate and share their information with other countries.

The second reflection concerns the need to adopt a global approach, not just limited to European countries, to improve vaccine uptake. In a globalised world, where viruses do not have a passport, it is crucial to have a clear broad vision and to adopt global strategies considering not only the different local contexts but a complex strategy that takes into account the close interconnections between all countries. In this context, global governance should be strengthened with the help of key international organisations.

One limitation of this exercise concerns the uncertainty of whether we have included all the literature on this topic (this is particularly the case for grey literature). Another limitation is that we did not carry out a specific survey of social media and other online information, which play a relevant role in the development of vaccine hesitancy. For the above reasons, this milestone is understood to be open, and it will be updated periodically before the end of IMMUNION.

This milestone is a first step towards the collection and evaluation of existing communication tools (second specific objective of WP6) and feeds into activities of the other WPs (in particular WP5, WP4 and WP2) to create awareness and involvement of the main stakeholders in recognising and combating vaccine hesitancy for both traditional and new vaccines.

Annexes included as in separate files:

Annex 1: first grid – peer-reviewed articles used to extract data (excel file).

Annex 2: description of extraction fields to fill in the first grid (word file).

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Appendix 1. Latvian surveys

Article 1 – http://petijumi.mk.gov.lv/sites/default/files/title_file/SKDS_Jun2021.pdf

A study of populations attitude on COVID-19

45% of survey participants indicated that they had already been vaccinated against COVID-19 with at least one dose. 3% admitted that they want to be vaccinated and will use the first chance to be vaccinated against COVID-19, 25% - that they could be vaccinated but still want to wait, 15% - that they do not want to be vaccinated against the coronavirus, but others can do as they wish, and another 10% are categorically against COVID-19 vaccination and consider that others should not be vaccinated either.

Among the most common reasons that prevent them from being vaccinated against COVID-19, respondents who are not vaccinated or do not intend to use the first opportunity to vaccinate mentioned considerations that offered vaccines are insufficiently tested (63%), it is not known how long vaccines will protect against COVID-19 and whether they will be effective against the new strains (60%) and indicated that they want to see how the vaccine works (what are the side effects, etc.) (53%).

In describing the factors that could influence vaccination readiness, it was most commonly vaccination would be improved if the vaccination point was close to home (31%, including 21% 'Significantly improved') or if vaccination points were also open on weekends (30%, including 15% 'Significantly improved'). Slightly less often a positive effect would be a longer vaccination point during working hours (25%, including 10% 'significantly improved') and the location of vaccination points for the event / place of interest to the respondents (20%, including 10% 'significantly improved'). It should be noted that the majority of respondents who do not want to be vaccinated or are categorically opposed to vaccination (also do not recommend it to others) noted that none of these aspects would improve their attitude against vaccination.

Article 2 –

https://www.rsu.lv/sites/default/files/imce/Projekti/VPP_COVID/2_darba_paka_gala_zinojums.pdf

A study on mental health and psychological sustainability and related factors in the population of Covid-19 during the pandemic/ future directions

12% of the respondents don't believe that the COVID-19 virus exists. Conspiracy theories were statistically significantly more prevalent amongst women, respondents living outside Riga who were divorced, unemployed and who had primary or secondary education. Respondents with depression more often considered that COVID-19 was developed in a laboratory, that COVID-19 is the result of a 5G antenna, and that COVID-19 is a sign of divine power to destroy our planet.

Lowest Covid-19 risk perception rates as well as lowest involvement compliance with epidemiological safety measures and preventive behaviour were by the population in the age group of 40 to 49 and people with lower level of education. People with lower psychological resilience, however, indicated that they were more afraid get sick with Covid-19, however, they also paid less attention to the precautions of the virus to reduce the prevalence.

Prevalent were beliefs that the vaccine against Covid-19 was ready before the virus spread and it was hidden from us for the benefit of pharmaceutical companies: 31.2% noted that this was possible. Only slightly more than half of the respondents (50.8%, n = 1326) did not trust this statement.



Article 3 – <https://www.spkc.gov.lv/lv/media/4297/download>

Health Behaviour among Latvian Adult Population, 2018

Diphtheria vaccination uptake is 49.8%. 30.2% have not received a vaccination for 10 years. When asked for reasons why not to vaccinate against diphtheria, 16.1% respondents responded that probability of falling ill is low; 29.4% were not informed of need to vaccinate; 14.2% responded that vaccination is harmful for my body; 16.3% said that vaccination may cause complications and 19.5% said that can't afford it (NB: it is covered by state).

Tick-borne encephalitis vaccination uptake is 26.2%. 58.1% of respondents have never been vaccinated against tick-borne encephalitis. When asked for reasons why not to vaccinate against tick-borne encephalitis, 25.1% respondents said that probability of falling ill is low and 17.5% responded that there are other ways avoiding the disease. 12.7% said that vaccination may cause complications; 11.1% - that it is harmful for the body. 31.9% responded that can't afford it.

Influenza vaccination "last year" uptake was 12,5%. 63.8% of respondents have never been vaccinated against influenza. When asked for reasons why not to vaccinate against influenza, 41,9% respondents said that there are other ways avoiding the disease; 16% responded that it may cause complications; 12.8% - that it is harmful for my body; 25.9% - that the vaccination is ineffective.

When asked for reasons why not to vaccinate against HPV, 27.7% respondents said that have not heard about such vaccination, 20% their decision would rely on doctors' suggestion, 22% would recommend daughter or relatives/friend's daughter to vaccinate; 10% would not recommend them to vaccinate.

Article 4 – *(online link unavailable)*

Study of monitoring children's immunization indicators and identifying causes of delayed vaccination in Latvia in 2015

The level of immunization required by the Public Health Guidelines (95%, against tuberculosis - 97%) in 12-month-old children is achieved against all infectious diseases scheduled in the vaccination schedule, with the exception of vaccination against pneumococcal infection (90.7%). In 24-month-old children, the target coverage level (95%) has not been reached for any of the vaccines included in the vaccination schedule and ranges from 79.3% (chickenpox) to 90.8% (measles, rubella, mumps). Main reasons for not vaccinated children: parents' refusals, contraindications. 77% - of the total number of unvaccinated children was due to parents' refusals (for 12M old children); 46.3% - for 24M old children.

17.8% of GPs considered that they had insufficient or outdated knowledge on vaccination issues. 23.7% said they had doubts or concerns about vaccination against influenza, 16.9% said they had doubts about vaccination against chickenpox, and 14.9% had doubts about vaccination against HPV. PHC specialists have the least doubts about diphtheria and tetanus (including combined vaccines against polio, whooping cough and hepatitis B), as well as vaccination against tuberculosis, measles, rubella and mumps. Slightly more than half of PHC specialists were afraid of possible complications after vaccination.

Vaccination against tetanus, polio, diphtheria, tuberculosis and whooping cough was considered important. 65.5% of specialists had attended postgraduate training courses on vaccination or vaccine-regulated infectious diseases for the last time in the last two years. 13.9% of employees had attended postgraduate continuing education courses for the last time more than 3 years ago. Among PHC



specialists, 22.3% indicated that parents of children who refuse to vaccinate their child should be subjected to some form of punishment.

The main source of information for parents about vaccination issues was medical staff (GP or paediatrician, nurse or medical assistant), and most parents also trusted them the most. Parents more often noted that infectious diseases such as tuberculosis, diphtheria, hepatitis B, tick-borne encephalitis and tetanus can be a very serious threat to a child's health. Human papillomavirus infection, chickenpox and rotavirus infection were noted as infectious diseases that are less harmful to children.

From 148 primary healthcare specialists, 2 doctors think that vaccination is only marketing, 6 doctors think that it is better to gain natural immunity, 34.5% believe that people do not need vaccination if they have a healthy lifestyle and good health; 7 doctors think that vaccination may be needed only for risk groups. 18.2% doctors didn't have an opinion about vaccination against HPV- 18.2%, and 7.4% against flu. 27% had concerns of use of flu vaccine (because of effectiveness etc.), 16.9% had concerns of use of chickenpox vaccine -16.9%, 14.8% of use of HPV vaccine. 32.5% think that overall vaccines are not safe and effective. 12 doctors responded that vaccines are new, there is no experience with them, the results cannot be evaluated yet, and they have not been tested for a long time.

From 1879 parents of children till age 8, 18 mention as one of the reasons why not to vaccinate their children that vaccination is only pharmacy business, 35 had negative experience from others (family, friends etc.), 137 think that there is no need to vaccinate because a child has good health, 20 believe that there is an alternative to vaccination (natural immunity); 57 trust alternative medicine more; 80 trust homeopathy more. The main reasons for doubts (n=558) were safety, efficiency, quality (n=221) and fear of complications (n=181). 65 parents did not vaccinate their children because of costs and 168 did not receive recommendations from health professionals.

