Pandemic visits a doctor

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CHAPTER 8

Discussion

The recent pandemic of COVID-19 has significantly impacted public health and society, with some effects persisting long-term. It is unknown when future pandemics will occur, and it is essential to be prepared. The discussion of this thesis focuses on the three pillars of pandemic preparedness. The first part will focus on the **first pillar** (gaining insight in the spread of the disease) and the **second pillar** (healthcare resource planning) of the pandemic response. It further examines the association between coagulation, SARS-CoV-2 infection, and vaccination (**third pillar**). Insights gained from the COVID-19 pandemic may contribute to a broader understanding of population health and healthcare systems, which may enhance preparedness for future outbreaks.

PART 1: SURVEILLANCE OF THE SPREAD OF INFECTIOUS DISEASE WITH POPULATION DERIVED DATA ON SYMPTOMS AND BEHAVIOR AND THE APPLICATION OF THESE DATA.

Initially, the COVID RADAR app proved to be a success, attracting tens of thousands of participants. Early in the pandemic, it provided valuable insights, introduced innovative methods of delivering informative feedback to users, and achieved all of this while maintaining user privacy. It was particularly inspiring to witness the level of user engagement with the app, demonstrated through their responses to news updates and substantive questions sent via email.

"We use the COVID RADAR as supermarket radar.
We go to areas with low risk behavior and low symptom scores"

Chapter 2 demonstrates that the data from the COVID RADAR app were able to capture patterns similar to those observed in other data sources, such as number of nationally reported positive tests. This type of data is particularly relevant for primary care, as it captures early stages in the trajectory of an infection (during which a primary care physician is involved). In **chapter 3** we show with relatively simple models that, though not perfectly, this type of data is able to predict COVID-19 related primary care workload, outperforming predictions based solely on positive test results. Furthermore, the app also unintentionally served as a surveillance tool for tracking long-term symptoms following SARS-CoV-2 infection. In **chapter 4** we describe that 5% –10% of individuals experienced post-acute COVID symptoms, which persisted until at least 100 days after a positive test result. These symptoms clustered into distinct entities with varying incidences, patient characteristics and vaccination effects, suggestive of multiple mechanisms behind the development of post-acute COVID symptoms.

Though the data from the app yielded valuable insights, applying data from the COVID RADAR app as a surveillance method during the pandemic proved complex. This complexity stemmed from the selection of users and heterogeneity in user engagement, uncertainties about measurement validity, and challenges in effectively leveraging this type of data.

Selection of users and user engagement

As the pandemic progressed, the app's user cohort primarily consisted of individuals aged 60 years or older residing in the province South-Holland. This demographic skew naturally limited both the applicability and the generalizability of the app's data. Moreover, there was significant heterogeneity in user engagement, with varying levels of loyalty to app usage.

Rennie et al. investigated factors influencing engagement with this type of app by inviting participants from an existing cohort to use an app (Fenland cohort, N=4031, aged 45–70).(1) Their analysis revealed that app users were predominantly from higher socioeconomic classes and urban areas, a pattern consistent with selection observed in many health cohorts.(2) Qualitative analysis revealed that the primary factor driving participation was simply "familiarity with the app." Additionally, technical design played a critical role, with a streamlined and user-friendly onboarding process being essential. Sustained engagement was associated with age above 55, intermediate-level occupations, and above-average health but showed no correlation with gender or educational level. Notably, the severity of lockdown measures had no impact on engagement levels. Users emphasized the importance of integrating app usage into their daily routines.

These findings align with the result of several qualitative studies we conducted with end-users of the COVID RADAR app.(3) Another factor deemed valuable was the app's ability to provide personalized feedback, which likely enhanced public engagement during the pandemic. Small analyses, often conducted at users' request and subsequently shared within the app, were highly appreciated. This approach enabled the app to deliver nuanced and valuable information during the uncertainty of the pandemic.

In summary, sustained engagement with an app requiring regular questionnaire completion largely mirrors the selection patterns observed in other health cohorts. However, it also depends on factors such as the level of publicity, the accessibility of the application, and the ability to integrate its use into a daily routine. Monitoring this selection process with both quantitative and qualitative methods is crucial to optimize accessibility and inclusivity. These insights are valuable to take into account in the interpretation of data from such an app, or to decide on changes during usage, e.g. to include a broader set of participants.

Validity of measurements

Within the COVID RADAR app no standardized or validated questionnaires were employed. Symptom-related questions were based on expert knowledge and early descriptions of SARS-CoV-2 symptomatology. However, the included symptoms align with those identified as most predictive in several other studies,(4-6) although these vary by SARS-CoV-2 variant.(7) Furthermore, symptom trajectories corresponded to expected patterns around positive and negative test results **(chapter 2)**.

In the absence of validated instruments to assess the construct 'risk behavior,' the questionnaire was designed to quantify social distancing behavior (e.g., the number of persons within 1.5 meters per time period) and included questions about working from home, facemask usage, and exercise.(8) However, participants found it challenging to report the number of persons they had encountered within 1.5 meters, as reflected in numerous emails from users, as well as several other items. This limitation may have impacted the app's cognitive validity (i.e., whether the test or instrument is measuring what it is supposed to, based on how people understand and process the questions).

"What counts as 'a person within 1.5 meters'? Also cyclers passing by?"
"I've a question: Is walking the dog considered sporting?"

During the pandemic, instruments were developed to measure "risk" or "preventive" behaviors.(9, 10) These instruments often included not only social distancing but also hygiene behaviors (e.g., handwashing) and detailed questions about facemask usage. However, these questionnaires were typically based on local behavioral recommendations and were often too detailed for daily use, with a high burden on the users. Moreover, none of these instruments were designed to examine the relationship between measures of risk-enhancing behaviors and subsequent positive SARS-CoV-2 tests. However, other studies with less detailed repeated data compared with the COVID RADAR app found associations between risk-enhancing behaviors and subsequent positive SARS-CoV-2 tests.(11, 12)

The construct of "risk behavior" is more complex than represented in the COVID RADAR app. The probability of infection depends not only on the extent of social distancing but also on hygiene practices and the nature of contacts. The incorporation of additional elements into the app's instrument could have enhanced its value, particularly by exploring interactions between behavior and individual characteristics. However, such an expansion would likely make the questionnaire lengthier, reducing the app's usability.

In **chapter 2**, we observe an association between above-average risk behavior and a positive test, which suggests good criterion validity. However, it remains questionable whether this above-average risk behavior sufficiently discriminates between the two outcomes, and whether this association is truly causal. The actual result of this behavior—contact with a COVID-19 patient—correlated much more strongly with a positive test result and was therefore utilized in **chapter 3**. Although defining the relationship between risk behavior and infection risk at the individual level proved challenging, at the population level the link between measured behaviors and the proportion of individuals eventually exposed to a COVID-19 patient provides valuable insights into the current reproduction number and, consequently, the effectiveness of public health measures.(13)

In summary, despite that the questionnaire was not based on previously validated instruments, both symptom and behavior data in the COVID RADAR app proved valuable during the pandemic.

While symptom data were useful at both the individual and population levels, risk behavior data were most informative at the population level due to limited cognitive validity (i.e., whether users understand the questions correctly) and the narrow scope of items measured within the construct of 'risk behavior.' However, the outcome of such behavior—(recent) contact with a COVID-19 patient—proved highly valuable.

Application of app data

Beyond challenges inherent to the app itself, external factors also impeded the applicability and impact of the collected data. Collaboration with key institutions, such as the Municipal Health Services (GGD) and the National Institute for Public Health and the Environment (RIVM) which were tasked with managing the pandemic, was limited. Potential reasons for this, in addition to those mentioned earlier, included the overwhelming workload of these organizations, the presence of similar projects, and the possible misalignment of certain aspects of the COVID RADAR app with existing international definitions. Consequently, the integration of COVID RADAR data into pandemic policymaking was significantly constrained.

In Sweden and the United Kingdom, similar apps were developed to predict COVID-19 incidence and hospital admissions.(4, 5, 14) While these apps provided early insights into the pandemic's progression and highlighted differences in symptomatology between SARS-CoV-2 variants, their subsequent impact on policy remains unclear.(15) In the reports, data were used from app users who received test results to first fit a model predicting the individual probability of a positive SARS-CoV-2 test based on symptoms. These individual probabilities were then used to estimate the daily proportion of untested app users who might be infected.

At first glance, this methodology appears appropriate; however, it carries potential pitfalls, which is the reason we used a different approach in **chapter 3**. Specifically, transferring predicted probabilities of a positive test result from a tested population to an untested population introduces bias unless adjustments are made for the likelihood of being tested (which is not stable over time). Additionally, translating these individual probabilities into group risks introduces a form of 'reverse ecological fallacy' or 'exception fallacy'—when inferences about a group are based on observations of exceptional cases or individuals.(16-18) Instead, inferences about groups or populations should be drawn from data collected at the same level, appropriately weighted, standardized, and periodically recalibrated. Importantly, such inferences should never be interpreted as applying to an individual.

An unexpected valuable application of the app's data was its ability to identify patients experiencing long-term symptoms following an initial infection (**chapter 4**). Similar symptom monitoring apps also reported on the duration of symptoms after the acute phase.(19, 20) Additionally, this method of data collection provided insights into vaccine effectiveness and side effects.(21, 22) Furthermore, such data-gathering approaches could potentially be used to assess

the effects of public health measures, both on the pandemic's progression and broader aspects of psychosocial health.(23)

In summary, integration of data from a symptom-monitoring, population-based app into the existing information flow for policymakers is difficult to be effectively achieved during an acute event like a pandemic. Instead, systems should be designed and incorporated well in advance of such situations. Inferences should align with the level of analysis (individual to individual, population to population). Finally, these data platforms can be structured to allow secondary use, enabling the assessment of the (long-term) impacts of infections, measures, or the pandemic itself.

General considerations and recommendations for population based pandemic surveillance

It is important to emphasize that this method is simple, inexpensive, and accessible, and above all independent of healthcare utilization. This method of pandemic surveillance could be of high value in locations and periods with limited testing capacity, such as early in the pandemic or in lower income countries.(24) The voluntary self-reporting of symptoms and (risk) contacts naturally has drawbacks due to recall bias and missing data. However, when compared to other forms of surveillance (based on testing or healthcare utilization), it also offers several advantages. By focusing on symptoms instead of positive tests, surveillance bias is limited. An example of this type of bias is the increase in positive tests later in the pandemic, not as a result of a higher number of infections but due to the expansion of testing capacity. Later during the pandemic the proportion of positive tests increased substantially, not because of more SARS-CoV-2 but a change of behavior: self-testing prior to PCR testing. Additionally, self-reporting of symptoms and (risk) contacts provides an earlier picture of the pandemic's spread, as the data is not tied to healthcare utilization (situated lower in the pyramid, see Figure 1, p. 11).

Currently, the COVID RADAR app has been discontinued. However, the RIVM still maintains the "Infectieradar," a web-based platform, which shares many similarities with the COVID RADAR app.(25) Strong features of this website include the individual adaptability of the questionnaire and the ability to offer free testing provided by the RIVM. This testing option can be a significant factor in attracting more users, as it enhances the "What's in it for me" aspect. Furthermore, this data collection is effectively integrated into the overall data streams used by policymakers, which improves impact and utility of the data.

Building on the experiences with the COVID RADAR app, the "Infectieradar" can become even more valuable. Making the platform available as an app will lower the threshold for users to share data and improve overall usability. Additionally, a regular dialogue with users with individual feedback and small analyses upon request within the app enhances engagement. Insights from experts in citizen science may further support this approach by the incorporation of recent best

practices.(26) Although the current number of Infectieradar users is modest (10800 in April 2025), it can be easily scaled up in the event of a new pandemic. The presence of a pre-established communication plan for scaling up the application during such a time will prove prudent. The primary care network can play a key role in this expansion, as this type of data is particularly valuable in primary care settings.**(chapter 3)** The questionnaire can also be optimized for specific circumstances. It is crucial to strike the right balance between minimization of the burden on participants (keeping the questionnaire brief) and maximization of the relevance of the collected information. Our experience suggests that the question about "recent contact with a COVID-19 patient" provided more valuable data than all the questions related to the type of (risk-enhancing) behavior. This balance can be improved by a focus on the moment and type of contact with a potential contagious patient, and less on the different categories of risk-enhancing behavior.

PART 2: COAGULATION AND VENOUS THROMBOTIC EVENTS AS ADVERSE EVENTS FOLLOWING SARS-COV-2 VACCINATION AND SARS-COV-2 INFECTION.

During my internship as a general practitioner in 2021, I worked at a practice in The Hague, located in a beautiful neighborhood with an above average number of immigrants and people with a lower socioeconomic status. One of our tasks was vaccinating vulnerable groups against COVID-19.

A woman in her 50s from Sub-Saharan Africa came to the practice for her vaccine. Communication was challenging due to language barriers, particularly when explaining a consent form about sharing vaccination data with a thing called "the government". After some difficulty and several explanations from both the doctors as the supporting staff, she agreed.

Just before administering the vaccine, she asked, "Which vaccine will I get?"

When told it was AstraZeneca, she responded, in perfectly clear Dutch:

"Oh, I don't want that; it causes Cerebral Venous Sinus Thrombosis."

Venous thromboembolism and COVID-19 infection

Early in the pandemic a strong association between severe COVID-19 and venous thromboembolism (VTE) appeared evident, and the preventive use of anticoagulation in hospitalized acute COVID-19 patients was recommended.(27-29) A SARS-CoV-2 infection complicated by VTE is associated with a high rate of mortality, although it can be debated whether this high risk of death is a direct consequence of the VTE, or that the VTE is a sign of severe COVID-19.(30) The coagulation system is strongly linked to inflammatory responses, but other mediating mechanisms, such as hypoxia, immobilization, microvascular injury, or disseminated intravascular coagulation may also explain the strong association between COVID-19 and VTE.(31, 32) In **Chapter 5** we describe that in addition to these elements, an intrinsic hypercoagulable potential prior to infection is associated with an increased risk of severe disease. While these data specifically pertain to SARS-CoV-2

infection, intrinsic factors may also influence the severity of other infections, as thrombosis- and haemostasis-related complications were also previously observed during the Spanish Flu (33) and after current severe influenza infections.(34-36) Further research can expand our knowledge of this increased intrinsic risk, which may be influenced by genetic factors.(37, 38) Promising pathways from prior research are via ACE-2, Factor V Leiden (R506Q) and several other genes found via Mendelian Randomization (ABO, ADAMTS13, FUT2).(39-41)

Venous thromboembolism and SARS-CoV-2 vaccines

Later in the pandemic during the vaccination campaign, a potential link between COVID-19 vaccination and VTE emerged.(42-44) In **Chapter 6**, a small, transient increase in coagulation parameters is reported that was observed following administration of a mRNA-type SARS-CoV-2 vaccine. This increase was associated with the inflammatory response, underscoring the important link between the coagulation system and inflammation. Notably, reduction of the dose by a different route of administration diminished the vaccine's impact on both the inflammatory response and coagulation parameters, without compromising its protective efficacy. This finding may explain the lower incidence of systemic side effects observed with intradermal vaccination compared with intramuscular administration in this trial.(45) Future research should explore the potential for adapting current vaccine administration routes to reduce adverse events. Additionally, dose reduction can enhance vaccine availability, which was the original reason underlying the trial, to promote equity and accelerate progress toward herd immunity (**third pillar of pandemic preparedness:** fast development of vaccines).(46)

In Chapter 7 we present results of the TERA-study that showed that there is indeed an association between several SARS-CoV-2 vaccines and VTE. Our results indicate that mRNA-type vaccines were not or at most mildly associated with an increased risk of VTE. The vector based vaccines were associated with an increased risk of VTE, with relative risk estimates ranging between 1.5 for the AZD1222 vaccine to 2.9 for the Ad26.COV2.S vaccine. In addition, we show that confounding due to the selective vaccination of individuals with specific risk factors for both severe COVID-19 and VTE may explain the conflicting results observed in ours and other observational studies.(47-51) For example, the mRNA-1273 vaccine was associated with an increased risk of VTE; however, in the absence of VTE risk factors, this risk returned to baseline. The increased risk after this vaccine in the overall analyses may be explained by the preferential vaccination of individuals with risk factors with this vaccine, which was the case in the Netherlands.

The fact that there was no increased risk for these adverse events detected in the original randomized controlled trials could be explained by the low VTE risk and a lack of power.(52) Even in a meta-analysis, that combined six RCTs including ~70 000 participants per arm, the power to detect a risk ratio of 1.5 was less than 20%. Despite this, the authors concluded there was no increased risk of VTE after SARS-CoV-2 vaccination. From our study, it became clear that in 2021, under the circumstances in the Netherlands during a large pandemic, even though vaccination

did lead to thrombotic events, more cases of thrombosis were prevented by vaccination than caused by it. In fact, under the scenario that everyone had been vaccinated with the vaccine associated with the highest risk of VTE, VTEs were still prevented overall. This raises the question whether it is relevant to focus solely on this type of adverse event in the context of another more urgent and acute problem, such as a pandemic. Of course, this balance may be viewed differently when discussing it outside the context of an active pandemic, as is currently the case with booster vaccinations or with flu vaccinations.

Surveillance of adverse events of vaccines during a pandemic

In the Netherlands, the Lareb Institute is responsible for detecting and reporting drug- and vaccine-related adverse events. A reporting portal is in place through which both healthcare professionals and patients can report potential side effects. By comparing the number of reported cases with the expected incidence (background incidence) of the relevant symptoms or conditions, the Lareb Institute assesses whether a particular adverse event occurs more frequently than anticipated in individuals receiving the medication (observed vs expected analysis).(53)

While healthcare providers are legally obliged to report these adverse events (54), underreporting has been observed in practice.(55) This is taken into account in the analyses by Lareb by issuing a signal at a relative risk of >0.8 instead of >1.(56) However, increased media attention regarding the potential risk of VTE following vaccination may have made physicians more likely to report these adverse events, leading to an earlier detection of a potential signal.(57-59) The level of reporting is also affected by the "Weber-effect", i.e., an increase in adverse effect reporting in the first period after approval of a drug, resulting in earlier detection of a potential signal. (53, 60) However, there are more factors that may influence the degree of reporting. The likelihood of a healthcare professional identifying and reporting a potential adverse event increases when the same physician both prescribed the medication and diagnosed the adverse event. In the Netherlands, general practitioners administered the AstraZeneca vaccine. A case of VTE diagnosed by the general practitioner may have been more frequently perceived as associated with the AstraZeneca vaccine, and subsequently reported, than VTE following vaccination performed by other institutions.

Though the current system via Lareb is able to measure the number of reported adverse events after vaccination,(53) due to these biases it is not able to measure the causal link between vaccination and adverse events (such as VTE). For this, more in depth and detailed studies are needed, with adjustment for confounding factors and appropriate controls.

The case-control vs self-controlled case series vs. cohort

In studying the association between SARS-CoV-2 vaccines and the risk of VTE, we specifically opted for a case-control design, rather than the self-controlled case series (SCCS) design that has

been conducted frequently in recent years for studies on vaccine-related adverse events.(61) In the SCCS design, individuals who experience an event serve as their own controls by comparing the frequency of exposure during a specified period just before the outcome with the frequency during a period more distant in time from the outcome (either before or after). This design is efficient, and time-invariant confounding factors are inherently controlled. However, unadjusted time-varying factors may introduce bias in a SCCS design. More importantly, the design assumes the absence of specific associations between the outcome and the probability of subsequent exposure. If this assumption is violated, a common solution is to implement a 'pre-exposure period,' during which time is excluded from the reference category. However, determining the length of this period is arbitrary and context-dependent, yet it can influence the magnitude of the bias.(62) In the study the relationship between SARS-CoV-2 vaccination and VTE, this assumption is likely not to hold. After the potential link between SARS-CoV-2 vaccines and VTE became apparent, VTE (the outcome) may have emerged as a relative contraindication for SARS-CoV-2 vaccination (the exposure). However, individuals with VTE related to risk factors also associated with severe COVID-19 might also have been more likely to receive vaccination. And finally, VTE associated with SARS-CoV-2 infection may have led to a lower likelihood of vaccination after VTE, as immunity from infection would already protect these individuals. In summary, numerous factors could influence the relationship between the outcome and subsequent exposure in varying directions and over different time periods (which in addition could differ for each type of SARS-CoV-2 vaccine), which severely compromises the determination of an appropriate 'pre-exposure period'.

We opted for a case-control design, rather than a cohort design, because of two reasons: feasibility and the impact of misclassification. Starting a new cohort for this research question is not feasible. The incidence of VTE is approximately 1 in 1000 per year or 1 in 12 000 per month—the risk period following vaccination. To detect a twofold increase in risk after vaccination during a four weeks time interval in a cohort study design with 80% power, two groups of approximately 300 000 individuals each (one vaccinated and one unvaccinated) would be required. While such a study is generally impractical for most types of vaccinations, it was theoretically feasible during the SARS-CoV-2 vaccination campaign. About 80% of the population was vaccinated, and their vaccination was documented in a national register. Several studies with this design have been published, though some of them were not sufficiently powered.(63-66)

A cohort design is only feasible when based on register-based data. However, registration of the exposure, vaccination, is not perfect. In the Netherlands, the primary contributor to misclassification of vaccination was that vaccination registration was only possible with the patient's consent, which was not granted in approximately 7% of cases.(67) As a result, 7% of vaccinated individuals were not recorded as such and were instead classified as unvaccinated. In 2021, according to official records, 84% of adults in the Netherlands were vaccinated. However, the actual vaccination coverage was closer to 90% (+~7%). This misclassification had a particularly

significant impact on the unvaccinated cohort, reducing its proportion from 16% to 10%, meaning that, in reality, one in three individuals classified as unvaccinated had actually received a vaccine in 2021.

The impact of this misclassification on study results depends on the chosen control group. If the control group consists of individuals for whom no vaccination was registered in 2021,(65) in fact one third of them was exposed to a vaccine. In a design that uses person time, where unvaccinated and vaccinated individuals until they were vaccinated contributed to 'control time',(63) 6% of this control time would actually be risk time (see table 1). In both examples this would result in a underestimation of the true effect. In addition, misclassification of the outcome and confounders (which is also likely to happen in a register) would inevitably contribute to an increase of the magnitude of this bias.(68)

Table 1: Effect of exposure misclassification, assuming a true relative risk of 2. If 7% of vaccinated individuals are not registered as vaccinated, this result in a misclassification of 6% of 'control time'.

	Registered (93% correct)				
	28d risk		93%		
NL 18+	14 000 000	**Risk**	**Control**		
Vaccinated	11 700 000	84%	897 534	5 401 233	
Unvaccinated	2 300 000	16%	0	2 300 000	
	Total patient time		897 534	7 701 233	100
	True patient time		897 534	7 227 132	94%
	False patient time		0	474 101	**6%**
	Incidence rate true		0.002	0.001	
	Incidence rate false		0.001	0.002	
	Number of events		1795	8175	
	Incidence rate measured		0.002	0.00106	
	Incidence rate ratio (biased)			1.88	
	Reality (100% correct)				
	28d risk		100%		
NL 18+	14 000.000	**Risk**	**Control**		
Vaccinated	12 580 645	90%	965 091	5 807 777	
Unvaccinated	1 419 355	10%	0	1 419 355	
	Total patient time		965 091	7 227 132	
	True patient time		965 091	7 227 132	
	False patient time		0	0	
	Incidence rate true		0.002	0.001	
	Incidence rate false		0.001	0.002	
	Number of events		1930	7227	
	Incidence rate measured		0.002	0.001	
	Incidence rate ratio (true)			2	

To address the previously mentioned challenges—violations of assumptions inherent to the SCCS design, the effects of misclassification, and the superior efficiency—we opted for a case-control

design. However, it should be noted that this design is not without potential bias either. Controls were selected from a random sample of Dutch residents who participated in a cohort regularly responding to questionnaires. This may have resulted in a selection of people who do not fully represent the "source population." Additionally, because controls could only be selected if they survived, it was not possible to assess the risk of death due to (vaccine-induced) VTE, which may have led to the selection of less severe cases that survived after experiencing VTE.

Finally, as with all case-control studies, there is a potential for recall bias, which is also a misclassification of exposure. Recall bias means that cases are more likely to remember their exposure than controls, which will result in an overestimation of the true effect. However, in the TERA-study we primary used data from the national vaccination register. Only if no vaccination was registered, we used data from the questionnaire. This method reduced the potential impact of both recall bias from questionnaires and measurement errors leading to misclassification in registries.

In the TERA study, we found a discrepancy between hospital records and self-reported data from questionnaires. Therefore, we used a similar approach — combining data from questionnaires and registers — for confounding factors such as hospitalization, immobilization, and cancer. This discrepancy between recorded and self-reported data was also evident for major diagnoses, such as cancer, a finding consistent with prior research.(69) In the TERA study, to verify VTE diagnoses, we used both hospital data and questionnaire responses. Among 1016 individuals who completed the questionnaire and had a registered VTE diagnosis in 2021, over 150 reported no VTE. After confirmation through chart review, only 73 of these cases were found indeed not to have had a VTE. Combining multiple data sources can help mitigate this issue, though some measurement error will inevitably remain.

Comparison of methods of surveillance of adverse events of vaccines during a pandemic

In the study by Pottegård et al., a register-based cohort design was employed, and the researchers used a historical background incidence as a 'control group'.(42) The use of background incidences during a pandemic can be problematic, as the pandemic itself acts as a "background factor" that may influence the incidence of adverse events.(70) This is particularly pertinent for VTE following COVID-19 vaccinations. While Pottegård et al. relied on a historical background incidence, this approach does not account for the numerous secondary effects of the pandemic that could impact VTE incidence. These include lockdowns, changes in the incidence of other infectious diseases, and the consequences of delayed medical care. Failing to account for these effects—or their results—may lead to biased estimates. Despite these theoretical constraints, this study, limited to the AstraZeneca vaccine, identified relative risks similar to those reported in the TERA case-control study, with similar patterns observed across subgroups—higher risks noted particularly among younger individuals and women.

Using similar (Scandinavian) data sources as Pottegård et al. but with a SCCS design, Berild et al. also identified a substantially increased risk of VTE following administration of the AstraZeneca vaccine, particularly among young individuals and women.(71) Additionally, small risk increases were observed after administration of the Pfizer and Moderna vaccines, primarily among older individuals (aged >50) (see table 2). These patterns align with the estimates we found in the TERA case-control study. However, in a post-hoc analysis using femoral fracture as a "negative control" event, the authors demonstrated the impact of violations of the assumptions underlying the SCCS design, which resulted in estimates suggesting a doubling of the risk of femoral fracture following SARS-CoV-2 vaccination (which is unlikely). The authors caution that small positive associations in an SCCS design should be interpreted with care and argue that the observed associations for Pfizer and Moderna vaccines are likely invalid.

Comparing the signals identified by Lareb in their observed-versus-expected analysis with the relative risks found in the TERA case-control study, similar patterns of relative risks were observed for the AstraZeneca vaccine (overall increased risk, particularly among women and younger individuals; see table 2).(56) Additionally, for the Moderna vaccine, adverse events were reported more frequently among men than women in both the Lareb and TERA studies. However, compared with TERA, Lareb reports lower relative risks following almost all vaccines, accept the AstraZeneca vaccine. This can be explained by the difference in media coverage about the VTE side effects of AstraZeneca vaccine, compared with these other two vaccines, resulting in less underreporting for the AstraZeneca vaccine than the other vaccines.

Table 2: Relative risk estimates (Odds ratios, Observed/Expected, rate ratios) of the relation between SARS-CoV-2 vaccines and VTE in subsequent 28 days, in different studies using different design and data sources.

		Pfizer	Moderna	AstraZeneca	Johnson & Johnson
TERA	All	1.0	1.4	1.5	2.9
Odds ratios	Men	0.8	1.7	1.3	4.4
	Women	1.2	1.1	1.8	1.6
	<60	1.1	1.0	2.0	3.5
SCCS (71)	All	1.1	1.3	2.0	X
Rate ratios	Men	1.1	1.3	1.5	X
	Women	1.1	1.2	2.5	X
	<60	1.0	1.3	3.0	X
Lareb (56)	All	0.1	0.2	0.5	0.4
O/E	Men	0.1	0.3	0.4	0.4
	Women	0.1	0.2	0.6	0.4
	<60	0.2	0.2	1.2	0.4

General considerations and recommendations for the surveillance of adverse events of vaccines during a pandemic

As outlined in the previous section, in the surveillance of adverse events, the O/E (Observed-to-Expected) design tends to underestimate risks due to underreporting, the extent of which varies and can significantly affect estimates. As such, it is suitable primarily as a broad signal detection tool. For interventions administered to a large proportion of the population (e.g., vaccines, exceeding 80% coverage), even small differences in risk may have substantial impacts, with varying effects across population subgroups. A more precise estimation of such (stratified) risks can be achieved with a SCCS design. However, this approach is effective only for detecting large effects when assumptions are violated—something that frequently occurs. A prospective cohort design is often less feasible, and suffers problems due to the use of concurrent or historical background incidence rates and biases introduced by the misclassification in register data. A case-control approach, leveraging both register data and data collected for research purposes, is best suited for measuring and adjusting for confounding factors.

Effective communication of vaccination risks and benefits to the general public

Vaccination of the majority of the population is the most effective method to rapidly emerge from a pandemic situation (**third pillar**). A pandemic (such as COVID-19) will probably be caused by a novel opportunistic agent for which no vaccine is initially available. Such a vaccine must be newly developed. Consequently, precise information on the incidence of adverse events in specific populations associated with this newly developed vaccine is absent at the start of a campaign. However, given the international emergency, in the case of an effective vaccine, relatively rare adverse events, undetected in well-conducted randomized controlled trials, will rarely outweigh the substantial benefits of vaccination for the complete population. Thus, it would be unethical to delay vaccination until certainty about all possible (rare) adverse events is achieved. It is crucial that the public can understand this rationale and assess these risks themselves, ultimately leading to a willingness to be vaccinated.

Clear communication regarding the efficacy and potential side effects of vaccines is essential, as the effectiveness of vaccination programs relies on achieving high participation rates within the population. During the COVID-19 vaccination campaign, widespread concern arose among significant segments of the population concerning potential side effects of the vaccines. This concern delayed the campaign and may have contributed to a lower than desired vaccination rate. Furthermore, these concerns about the SARS-CoV-2 vaccines have also undermined trust in other vaccines, as evidenced by the declining participation rates in other vaccination campaigns in the Netherlands since the COVID-19 pandemic.(72)

Within the framework of shared decision-making, effectively communicating the benefits and risks of vaccination is complex, even in the absence of the urgency of a pandemic. A well-informed

patient must understand both relative and absolute risks, weigh individual risks against benefits for the broader population (a trait increasingly uncommon in today's individualistic society), and also resist the influence of the "prevention paradox." Even highly educated individuals often struggle with the latter:

"I've received the flu vaccine for years, but it only makes me sick, and I've never had the flu."
- Many of my colleagues working in hospitals and academia-

Since vaccination is one of the most cost-effective forms of modern healthcare, it is essential to prioritize research and education in the area or risk communication.(73, 74) Previous studies indicate that public discussions about specific adverse events should not focus on the accuracy or inaccuracy of their causal relationship with the vaccine. Instead, emphasis should be placed on the severity of the disease that is being prevented.(75) A compelling narrative is more impactful on the general public than presenting relative risk figures. Furthermore, it is crucial to build immunity against misinterpretation and misinformation.(76) As a familiar and trusted figure, the general practitioner could play a pivotal role in guiding and educating the public.

CONCLUDING REMARKS

Now that the COVID-19 pandemic is behind us, important work begins. We have learned that being well-prepared is essential. During the acute phase of the pandemic, it is difficult to establish a high-quality population-based syndromic surveillance system. However, such a system is immensely valuable for gaining early insights into the pandemic's progression (**first and second pillars**). These pillars prioritize collaboration and require the avoidance of competition. To ensure the **third pillar** is robust, a sufficiently large portion of the population must be willing to receive a vaccine. Clear communication about the (potential impact of) adverse events, but more importantly about the benefits of vaccination, should not be reserved for times of crisis.

A shift in mindset may also be necessary, moving the focus from the individual to the population. It is not "What's in it for me?" but "What's in it for us?" While the focus on the individual has brought remarkable advancements (personalized medicine, inclusive care), we must also recognize the limitations of this perspective. The individual perspective is constrained not only in scope but also in time. I may not personally benefit from the efforts we make now for pandemic preparedness, but for us as a society, these efforts will undoubtedly prove vital in the future. This need for collective thinking extends beyond infectious diseases to other health challenges and future threats, such as an aging population and issues related to planetary health.

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