

SUPPLEMENTARY DATA

Part I – Power calculation summary for different scenarios

In the earliest stage of this research, power size calculations were performed, and it was evident the Nivel database would best suit our study purposes. Nivel systematically tracks the Dutch health system and report sudden changes in disease patterns, for which it weekly collects –anonymized– data from 350 ‘surveillance’ general practices in the Netherlands. Nivel monitors incidence of different types of diseases, such as circulation of infectious diseases. For patients that were subscribed to participating general practices in the Nivel surveillance system, medical records were tracked, such as previous diagnoses and classifications used for symptoms associated with COVID-19. For a subgroup of 40 ‘sentinel’ stations (that belonged to the total group of 350 general practices), PCR-COVID-19-tests were taken, and it was investigated which group would meet this study’s power (80%) requirements, as described below.

Power calculations

In the period from 10 March to 22 November 2020, Nivel reported that Dutch general practitioners recorded over 123,000 GP-diagnosed COVID-19 patients during COVID-19 pandemic. On the basis of these data and the further expected course, it was estimated that in the Nivel practices, in the period from 10 March to the start of this statistical analyses (22 November 2020), there would be more than sufficient cases to detect a relative risk reduction of 25% after influenza vaccination for patients with GP-diagnosed COVID-19, applying an alpha of 0.05 and a power of 0.80 in two-tailed testing (SPSS version 26.0, Armonk, NY: IBM Corp.). We aimed for a 25% risk reduction for GP-diagnosed COVID-19 after influenza vaccination, after a recent study had shown a risk reduction of 39% ($p=0,001$) on COVID-19 incidence for those had received influenza vaccination during the 2019/2020 winter season, compared to those who had not received it.⁽¹⁾ This was done in a study population of 10631 Dutch hospital employees with a lower age (average age of 41 years for the COVID-19 positive group and 42 years for the COVID-19 negative group).⁽¹⁾

We executed power calculations for different scenarios to explore which subjects should be included in this study [Supplementary part II].

Table SI-1 Power calculations for study population scenarios.

Scenario	Inclusion	Power
A	Nivel40, COVID-19 test-positive patients only	49.4%
B	Nivel40, COVID-19 test-positive and suspected patients	96.3%
C	Nivel350, COVID-19 test-positive patients only	99.1%
D	Nivel350, COVID-19 test-positive and suspected patients	100%
E	Nivel350, COVID-19 test-positive patients aged 60 years and older	97.7%
F	Nivel350, COVID-19 test-positive and suspected patients aged 60 years and older	100%

For all scenarios, two-sided testing was used, with alpha 0.05, beta 0.20 and a 25% relative risk reduction for GP-diagnosed COVID-19 to be minimally detected.

It was concluded that for the data from 350 Nivel surveillance stations, a high power would be achieved, either for the test-positive patients only, or for a combination of COVID-19 test-positive patients and GP-diagnosed COVID-19 patients. For the subgroup of patients aged 60 years and older, a high power would be achieved as well. For the 40 Nivel Sentinel stations, a high power could be achieved when including both test-positive and suspected patients. Using the Nivel350 group was therefore the safest option to reach sufficient study power.

Part II – Elaboration of different scenarios

In this section, the power calculations are described for different scenarios and which were executed prior to the retrieval of the database in November 2020. In all scenarios, group 1 corresponds with the group that was vaccinated against the influenzavirus. Group 2 corresponds with the unvaccinated group. To reach a relative risk reduction of at least 25%, the incidence of group 1 is 75% of group 2 (base population). For the power calculations as described below, which were done in July 2020, it was assumed that there were no proportional differences in GP-diagnosed COVID-19 incidence between unvaccinated and vaccinated groups between the situation in July 2020 and that in November 2020.

The following data were accessed when the study protocol was written, on 21 July 2020:

- a. COVID-19 cases till 21 July 2020 (total population of 17.28 million inhabitants)
- GP-diagnosed COVID-19 = 123,500 = 0.7147% (of 17.28 million) (2, 3)
 - Test-confirmed COVID-19 cases: 52,073 = 0.3013% (4)
 - o 50% aged \geq 60 years 26,036
 - Hospitalized 11,902 (4)
 - o 70% aged \geq 60 years 8,331
 - Died (positively tested) 6,136 (4)
 - o 97% aged \geq 60 years 5,952
- b. Vaccinated group:
- 18% (= 3.1 million) (5)
 - At-risk group = 50% (5)
 - All aged \geq 60 years old = 55% (5)
 - o 4.44 million persons that represent 25.7% of the Dutch population: $0.55 \times 4.44 = 2.4$ million vaccinated persons aged 60 years or above (2)

'Nivel350' (representing 350 surveillance family care practices)

- Base population: 1.3 million (approximately 8% of the total Dutch population)

'Nivel40' (representing 40 Sentinel stations)

- Base population: 130,000 (approximately 8% of the total Dutch population)
- o Including those aged \geq 60 years: 34,560
- 18% vaccinated against influenza 23,400
 - o Including those aged \geq 60 years: $0.55 \times 34,560$ 19,008
- Total number of unvaccinated: $130,000 - 23,400 = 106,600$
- GP-diagnosed COVID-19 929 (0.7147% of 130,000)
- Test-confirmed COVID-19 392 (0.3013% of 130,000)
 - o aged \geq 60 years (50%): $181/34,560 \times 100\% = 0.524\%$
- Suspected plus test-confirmed cases: 1321 (1.0160% of 130,000)
 - o aged \geq 60 years (50%): $6,601/34,560 \times 100\% = 19.1\%$
- Hospitalized: 96 (0.074%)
- Died (test-confirmed COVID-19 cases): 48 (0.037%)

For the power calculations, *Clin Calc* software was used.(6)

- An alpha of 0.05 was used to detect significant risk reductions of at least 25%.
- Assumptions: for the unvaccinated group, the cumulative incidence is the incidence of the base population. The incidence of group 1 (vaccinated) is 75% of the incidence of group 2 (unvaccinated).
- Prior to the power calculations, predictions were made (in July 2020) for the number of cases in November 2020 and which are described in Supplementary Part III.

Scenario A. 'Nivel40': test-confirmed COVID-19 cases

Number of cases till July 2020: 360 (base incidence: 0.3013%) (3)

Table SII-1 Power calculation outcomes scenario A.

Post-hoc Power	
49.4%	
Study Parameters	
Incidence, group 1	0.2260%
Incidence, group 2	0.3013%
Subjects, group 1	23400
Subjects, group 2	106600
Alpha	0.05

Note. Dichotomous endpoint, two Independent Samples Study.

Scenario B. 'Nivel40': test-confirmed COVID-19 cases and GP-diagnosed COVID-19 cases

Number of cases till July 2020: 1321 (base incidence: 1.0160%) (3)

Table SII-2 Power calculation outcomes scenario B.

Post-hoc Power	
96.3%	
Study Parameters	
Incidence, group 1	0.762%
Incidence, group 2	1.0160%
Subjects, group 1	23400
Subjects, group 2	106600
Alpha	0.05

Note. Dichotomous endpoint, two Independent Samples Study.

Scenario C. 'Nivel350': test-confirmed COVID-19 cases

- Prediction of number of COVID-19 test-confirmed cases in week 47: $2.59\% / 100\% \times 67,625 = 1.751$ (3).
- Predicted base population: 0.0259×17.28 million = 447,500 (2,3)
 - o Therefore, the incidence is $1,751/447,500 = 0.0039128$.
- Vaccinated: $18\% \times 447,500 = 80,550$ (2,5)
- Unvaccinated: $82\% \times 447,500 = 366,950$ (2,5)

Table SII-3 Power calculation outcomes scenario C.

Post-hoc Power	
99.1%	
Study Parameters	
Incidence, group 1	0.29346%
Incidence, group 2	0.39128%
Subjects, group 1	80550
Subjects, group 2	366950
Alpha	0.05

Note. Dichotomous endpoint, two Independent Samples Study.

Scenario D. 'Nivel350': test-confirmed COVID-19 cases and GP-diagnosed COVID-19 cases

- Prediction of number of GP-diagnosed COVID-19 cases during COVID-19 pandemic in week 47: $2.59\% / 100\% \times 170,156 = 4,407$ (3).
- Therefore, the incidence of test-confirmed COVID-19 cases plus GP-diagnosed COVID-19 cases = $(1,751 + 4,407) / 447,500 = 0.01376089 = 1.376089\%$.
 - o P1 is 75% (based on expected risk reduction of 25%): 1.032067% .
- Vaccinated: $18\% \times 447,500 = 80,550$ (2,5)
- Unvaccinated: $82\% \times 447,500 = 366,950$ (2,5)

Table SII-4 Power calculation outcomes scenario D.

Post-hoc Power	
100%	
Study Parameters	
Incidence, group 1	1.032067%
Incidence, group 2	1.376089%
Subjects, group 1	80550
Subjects, group 2	366950
Alpha	0.05

Note. Dichotomous endpoint, two Independent Samples Study.

Scenario E. 'Nivel350': test-confirmed COVID-19 cases, group ≥60 years old

The group ≥ 60 years old represents 25.671% of the total Dutch population.(1) On average, 55% gets vaccinated against influenza.(5)

- N1 = number of vaccinated individuals aged ≥ 60 years:
 $0.25671 \times 447,500 \times 0.55 = 63,180$
- N2 = number of unvaccinated individuals aged ≥ 60 years:
 $0.25671 \times 447,500 \times 0.45 = 51,690$
- $N1 + N2 = 114,870$
- 50% of 1751 test-confirmed cases = 876
 - o $876 / 114,870 = 0.0076260$ (p2; base incidence)
 - $p1 = 75\% = 0.0057195$

Table SII-5 Power calculation outcomes scenario E.

Post-hoc Power	
97.7%	
Study Parameters	
Incidence, group 1	0.57195%
Incidence, group 2	0.76260%
Subjects, group 1	63180
Subjects, group 2	51690
Alpha	0.05

Note. Dichotomous endpoint, two Independent Samples Study.

Scenario F. 'Nivel350': test-confirmed COVID-19 cases and GP-diagnosed COVID-19 cases, group ≥60 years old

- 50% of test-confirmed and GP-diagnosed COVID-19 (1,751 + 4,407) = 3,079
 - o $3,079 / 114,870 = 0.0268042$ (p2; base incidence)
 - $p1 = 75\% = 0.02010316$

Table SII-6 Power calculation outcomes scenario F.

Post-hoc Power	
100%	
Study Parameters	
Incidence, group 1	2.01032%
Incidence, group 2	2.68042%
Subjects, group 1	63180
Subjects, group 2	51690
Alpha	0.05

Note. Dichotomous endpoint, two Independent Samples Study.

Part III – Assumptions for power calculations

Predictions were made for the total number of COVID-19 cases in week 47 (when the analyses started) and which was based on the Nivel data which were accessible on 21 July 2020.⁽³⁾ The numbers on July 21st were retrieved from the data from 350 general practices.⁽³⁾ Every week, these practices provide epidemiological data for various conditions, and which are used by Nivel to monitor the incidence of certain diseases in the total population, such as infectious diseases.⁽⁵⁾ This surveillance system is also used to monitor the COVID-19 situation in the Netherlands.⁽³⁻⁵⁾

Number of confirmed and suspected COVID-19 cases in the period from 10 March 2020 (week 10) up to and included week 29 in 2020 (which is the moment of the power calculations):

- 52,073 confirmed COVID-19 cases (on 21 July 2020);⁽³⁾
- 123,500 COVID-19 suspected COVID-19 cases (on 21 July 2020).⁽³⁾

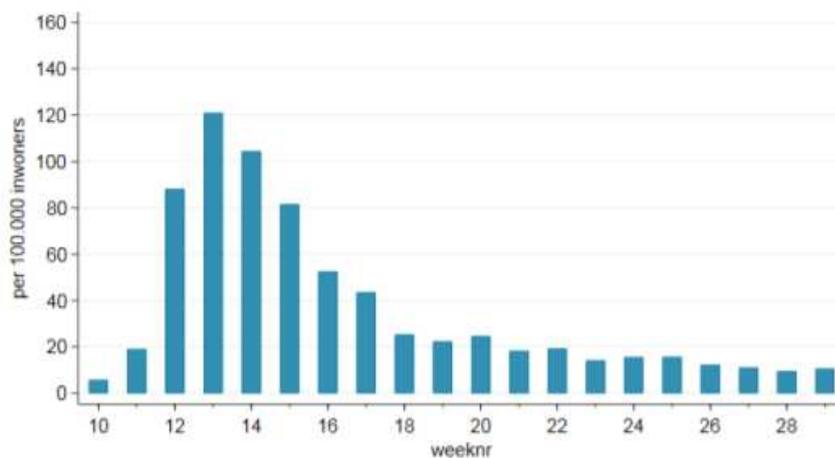


Figure SIII-1 Total number of patients with a first contact GP-visit because of COVID-19 related symptoms (excluding test-confirmed COVID-19), per 100,000 inhabitants.⁽³⁾

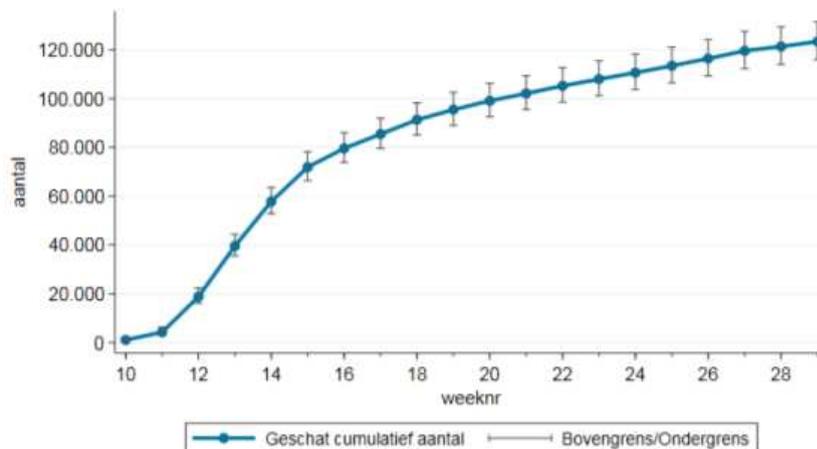


Figure SIII-2 Total number of patients with a first contact GP-visit because of COVID-19 related symptoms (excluding test-confirmed COVID-19), up to and included week 29 in 2020 (in the Netherlands) (including 95% confidence intervals).⁽³⁾

Assumptions and prediction of COVID-19 cases in week 47 (2020)

From week 47 in 2020, the analyses started. The number of COVID-19 cases were predicted, based on the available data in week 28 (2020).(3) The following was assumed for the time between period 28 up to and including week 47:

1. Every week, there will be added at least 5 new test-confirmed COVID19 cases (per 100,000 inhabitants);
2. Every week, there will be at least 15 GP-diagnosed COVID-19 cases during the COVID-19 pandemic (per 100,000 inhabitants).

Total Dutch population: estimated number of COVID-19 test-confirmed cases in week 47: $52,073 + ((5/100,000) \times 17,280,000 \times 18 \text{ weeks}) = 67,625$.

Total Dutch population: estimated number of - GP-diagnosed COVID-19 cases in week 47: $123,500 + ((15/100,000) \times 17,280,000 \times 18 \text{ weeks}) = 170,156$.

Estimation of total amount of COVID-19 cases (test-confirmed and GP-diagnosed cases) in the Nivel surveillance practices

Based on the *Monitor Vaccinatiegraad Nationaal Programma Grieppreventie 2018* (5), 163/440 general practices (37%) were included in the 2018 Nivel analyses. Inclusion criteria were based on the availability and quality of data as provided by the practices and which are available to the Stichting Nationaal Programma Grieppreventie (SNPG) for a >90% similarity between registered and declared vaccinations. In the Netherlands, there are approximately 5020 family care practices [5]. For 350 of them (the Nivel surveillance stations), there is provided weekly data, which are used by Nivel for their analyses. Taking into account the fraction 37% which was included in the Nivel database, it is expected that 130 practices are included for the 2019 Nivel analyses, and therefore, for this study.

Proportion Nivel practices, relative to total number of general practices in the Netherlands = $130/5,020 = 2.59\%$

Nivel surveillance practices: expected number of test-confirmed COVID-19 cases in week 47: $2.59\% / 100\% \times 67,625 = 1,751$

Nivel surveillance practices: expected number of GP-diagnosed COVID-19 cases during COVID-19 pandemic in week 47: $2.59\% / 100\% \times 171,800 = 4,407$

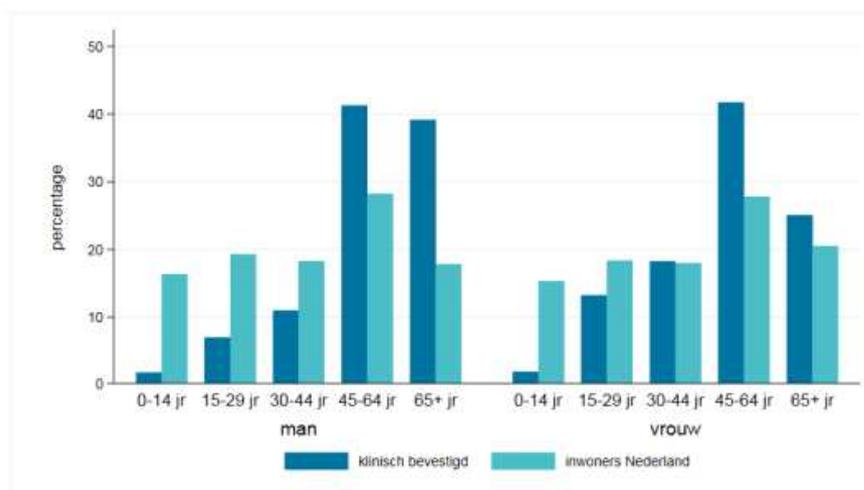


Figure SIII-3 Estimation of the percentage GP-diagnosed COVID-19 (in the Netherlands) for males and females, and the percentage distribution for the number of inhabitants in the Netherlands, per age group (week 10-21 2020).(3)

Part IV: Sensitivity Analyses

FIRST WAVE – GP-DIAGNOSED COVID-19

Table SIV-1 Hazard Ratios for GP-diagnosed COVID-19, adjusted for covariables, 10 March – 1 June 2020 (first wave) (n=223,580).

Covariable	GP-diagnosed COVID-19 Hazard Ratio	95% Confidence Interval
Influenza vaccination in 2019 (yes vs no)	1.19	1.04 – 1.36
Age group, relative to group 0-59 years		
60-74 years	0.97	0.82 – 1.15
75+ years	1.36	1.13 – 1.64
Cardiovascular disease (yes vs no)	1.27	1.09 – 1.47
Pulmonary disease (yes vs no)	1.38	1.17 – 1.62
Diabetes mellitus (yes vs no)	1.47	1.26 – 1.70
Impaired resistance to infections (yes vs no)	1.41	1.12 – 1.79
Chronic renal insufficiency (yes vs no)	1.39	1.09 – 1.77
Respiratory disorders by neurological conditions (yes vs no)	1.52	1.20 – 1.92
Number of acute respiratory infection consultations in 2019, relative to 0		
1	1.40	1.13 – 1.74
≥2	1.55	1.22 – 1.98

SECOND WAVE – GP-DIAGNOSED COVID-19

Table SIV-2 Hazard Ratios for GP-diagnosed COVID-19, adjusted for covariables, 1 June – 22 November 2020 (second wave) (n=222,580).

Covariable	GP-diagnosed COVID-19 Hazard Ratio	95% Confidence Interval
Influenza vaccination in 2019 (yes vs no)	1.13	1.05 – 1.22
Sex (female vs male)	1.09	1.02 – 1.17
Age group, relative to group 0-59 years		
60-74 years	0.60	0.56 – 0.65
75+ years	0.53	0.48 – 0.59
Diabetes mellitus (yes vs no)	1.24	1.13 – 1.35
Respiratory disorders by neurological conditions (yes vs no)	0.79	0.66 – 0.95
Number of acute respiratory infection consultations in 2019, relative to 0		
1	1.25	1.11 – 1.42
≥2	1.50	1.30 – 1.72

Part V: Mortality rates comparison between national data and data of this study

Table SV-1 Comparison of mortality rates between total population data and the primary care population-based cohort.

	Total population	Our data
Total group (males and females)		
65-79 years old	1.43%	1.08%
80+ years old	8.28%	4.82%
Males		
65-79 years old	1.73%	1.30%
80+ years old	9.21%	5.66%
Females		
65-79 years old	1.15%	0.87%
80+ years old	7.69%	4.25%

Note. This study was a primary care population-based cohort. Total population data from CBS included persons that were admitted in hospitals and nursing-home residences(7) and these persons were not part of our population.

REFERENCES – SUPPLEMENTARY DATA

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