Afspraak.start_week	GGD	Aantal get	Aantal pos	Percentage positief
2020-06-01	Dienst Gez	1477	55	3.7
2020-06-01	GGD Amst	4402	107	2.4
2020-06-01	GGD Braba	1809	37	2
2020-06-01	GGD Drent	991	7	0.7
2020-06-01	GGD Flevo	1271	15	1.2
2020-06-01	GGD Fryslá	1067	5	0.5
2020-06-01	GGD Gelde	2249	76	3.4
2020-06-01	GGD Gooi	910	1	0.1
2020-06-01	GGD Groni	1007	1	0.1
2020-06-01	GGD Haagl	3335	100	3
2020-06-01	GGD Hart	6418	140	2.2
2020-06-01	GGD Holla	2287	43	1.9
2020-06-01	GGD Holla	1401	9	0.6
2020-06-01	GGD IJssell	1415	17	1.2
2020-06-01	GGD Kenn	1351	19	1.4
2020-06-01	GGD Limbu	1496	20	1.3
2020-06-01	GGD Noor	1947	62	3.2
2020-06-01	GGD Regio	1222	7	0.6
2020-06-01	GGD Regio	5008	109	2.2
2020-06-01	GGD Rotte	2985	100	3.4
2020-06-01	GGD West	2059	43	2.1
2020-06-01	GGD Zaans	1034	13	1.3
2020-06-01	GGD Zeela	669	4	0.6
2020-06-01	GGD Zuid-I	2034	27	1.3
2020-06-01	Veiligheids	2177	39	1.8
2020-06-08	Dienst Gez	1478	18	1.2
2020-06-08	GGD Amst	4798	92	1.9
2020-06-08	GGD Braba	2517	40	1.6
2020-06-08	GGD Drent	1130	4	0.4
2020-06-08	GGD Flevo	1449	15	1
2020-06-08	GGD Fryslá	1405	15	1.1
2020-06-08	GGD Gelde	2090	17	0.8
2020-06-08	GGD Gooi	994	11	1.1
2020-06-08	GGD Groni	1163	5	0.4
2020-06-08	GGD Haagl	4118	112	2.7
2020-06-08	GGD Hart	7642	108	1.4
2020-06-08	GGD Holla	3389	62	1.8
2020-06-08	GGD Holla	1561	5	0.3
2020-06-08	GGD IJssell	1625	20	1.2
2020-06-08	GGD Kenn	1701	16	0.9
2020-06-08	GGD Limbu	1473	22	1.5
2020-06-08	GGD Noor	1999	39	2
2020-06-08	GGD Regio	1397	7	0.5
2020-06-08	GGD Regio	5609	80	1.4

2020-06-08GGD Rotte	4637	117	2.5
2020-06-08GGD West	2391	17	0.7
2020-06-08GGD Zaans	1011	22	2.2
2020-06-08GGD Zeela	824	2	0.2
2020-06-08GGD Zuid-I	1906	15	0.8
2020-06-08Veiligheids	2527	34	1.3
2020-06-15Dienst Gez	1333	9	0.7
2020-06-15GGD Amst	4998	58	1.2
2020-06-15GGD Braba	3047	21	0.7
2020-06-15GGD Drent	1403	3	0.2
2020-06-15GGD Flevo	1439	8	0.6
2020-06-15GGD Fryslá	1347	2	0.1
2020-06-15GGD Gelde	2066	11	0.5
2020-06-15GGD Gooi	1192	10	0.8
2020-06-15GGD Groni	1482	2	0.1
2020-06-15GGD Haagl	4568	70	1.5
2020-06-15GGD Hart \	8244	88	1.1
2020-06-15GGD Holla	3874	38	1
2020-06-15GGD Holla	1666	3	0.2
2020-06-15GGD IJssell	1829	15	0.8
2020-06-15GGD Kenn	2110	11	0.5
2020-06-15GGD Limbu	1478	7	0.5
2020-06-15GGD Noor	2182	38	1.7
2020-06-15GGD Regio	1721	8	0.5
2020-06-15GGD Regio	5914	60	1
2020-06-15GGD Rotte	4820	85	1.8
2020-06-15GGD West	2545	12	0.5
2020-06-15GGD Zaans	1208	14	1.2
2020-06-15GGD Zeela	705	3	0.4
2020-06-15GGD Zuid-I	1832	6	0.3
2020-06-15Veiligheids	2723	29	1.1
2020-06-22Dienst Gez	1655	8	0.5
2020-06-22GGD Amst	4264	50	1.2
2020-06-22GGD Braba	2820	9	0.3
2020-06-22GGD Drent	1461	1	0.1
2020-06-22GGD Flevo	1508	9	0.6
2020-06-22GGD Fryslá	1518	2	0.1
2020-06-22GGD Gelde	2050	17	0.8
2020-06-22GGD Gooi	1179	25	2.1
2020-06-22GGD Groni	1479	0	0
2020-06-22GGD Haagl	4641	62	1.3
2020-06-22GGD Hart \	7238	60	0.8
2020-06-22GGD Holla	3917	14	0.4
2020-06-22GGD Holla	1889	4	0.2
2020-06-22GGD IJssell	1947	10	0.5

2020-06-22	GGD Kenn	2142	5	0.2
2020-06-22	GGD Limbu	1551	2	0.1
2020-06-22	GGD Noor	2427	22	0.9
2020-06-22	GGD Regio	1497	5	0.3
2020-06-22	GGD Regio	6063	56	0.9
2020-06-22	GGD Rotte	4409	71	1.6
2020-06-22	GGD West	2376	8	0.3
2020-06-22	GGD Zaans	1084	2	0.2
2020-06-22	GGD Zeela	944	2	0.2
2020-06-22	GGD Zuid-I	1846	4	0.2
2020-06-22	Veiligheids	2936	8	0.3
2020-06-29	Dienst Gez	2016	4	0.2
2020-06-29	GGD Amst	4433	31	0.7
2020-06-29	GGD Braba	2553	11	0.4
2020-06-29	GGD Drent	1653	2	0.1
2020-06-29	GGD Flevo	1580	2	0.1
2020-06-29	GGD Fryslá	1814	6	0.3
2020-06-29	GGD Gelde	2382	6	0.3
2020-06-29	GGD Gooi	1256	20	1.6
2020-06-29	GGD Groni	1834	2	0.1
2020-06-29	GGD Haagl	5043	42	0.8
2020-06-29	GGD Hart	7808	62	0.8
2020-06-29	GGD Holla	3996	20	0.5
2020-06-29	GGD Holla	1978	2	0.1
2020-06-29	GGD IJssell	2081	12	0.6
2020-06-29	GGD Kenn	2190	11	0.5
2020-06-29	GGD Limbu	1666	2	0.1
2020-06-29	GGD Noor	3000	10	0.3
2020-06-29	GGD Regio	1594	8	0.5
2020-06-29	GGD Regio	6930	33	0.5
2020-06-29	GGD Rotte	5200	79	1.5
2020-06-29	GGD West	2703	15	0.6
2020-06-29	GGD Zaans	1113	3	0.3
2020-06-29	GGD Zeela	1257	4	0.3
2020-06-29	GGD Zuid-I	1987	11	0.6
2020-06-29	Veiligheids	3085	8	0.3
2020-07-06	Dienst Gez	2242	6	0.3
2020-07-06	GGD Amst	4879	44	0.9
2020-07-06	GGD Braba	3083	13	0.4
2020-07-06	GGD Drent	1659	4	0.2
2020-07-06	GGD Flevo	1621	2	0.1
2020-07-06	GGD Fryslá	1919	3	0.2
2020-07-06	GGD Gelde	2726	18	0.7
2020-07-06	GGD Gooi	1345	10	0.7
2020-07-06	GGD Groni	2082	3	0.1

2020-07-06	GGD Haagl	5570	59	1.1
2020-07-06	GGD Hart \	8606	52	0.6
2020-07-06	GGD Holla	4271	19	0.4
2020-07-06	GGD Holla	2109	3	0.1
2020-07-06	GGD IJssell	2201	11	0.5
2020-07-06	GGD Kenn	2301	11	0.5
2020-07-06	GGD Limbu	1623	1	0.1
2020-07-06	GGD Noor	3220	1	0
2020-07-06	GGD Regio	2071	5	0.2
2020-07-06	GGD Regio	8590	46	0.5
2020-07-06	GGD Rotte	5843	105	1.8
2020-07-06	GGD West	3064	28	0.9
2020-07-06	GGD Zaans	1284	6	0.5
2020-07-06	GGD Zeela	1471	23	1.6
2020-07-06	GGD Zuid-I	2155	5	0.2
2020-07-06	Veiligheids	3287	11	0.3
2020-07-13	Dienst Gez	2643	15	0.6
2020-07-13	GGD Amst	5654	130	2.3
2020-07-13	GGD Braba	3571	19	0.5
2020-07-13	GGD Drent	1904	10	0.5
2020-07-13	GGD Flevo	1749	2	0.1
2020-07-13	GGD Fryslá	2098	4	0.2
2020-07-13	GGD Gelde	3402	13	0.4
2020-07-13	GGD Gooi	1457	11	0.8
2020-07-13	GGD Groni	2374	2	0.1
2020-07-13	GGD Haagl	6707	101	1.5
2020-07-13	GGD Hart \	10596	52	0.5
2020-07-13	GGD Holla	5213	62	1.2
2020-07-13	GGD Holla	2567	22	0.9
2020-07-13	GGD IJssell	2403	18	0.7
2020-07-13	GGD Kenn	2425	34	1.4
2020-07-13	GGD Limbu	1990	3	0.2
2020-07-13	GGD Noor	3744	5	0.1
2020-07-13	GGD Regio	2375	7	0.3
2020-07-13	GGD Regio	10838	93	0.9
2020-07-13	GGD Rotte	6715	180	2.7
2020-07-13	GGD West	3664	69	1.9
2020-07-13	GGD Zaans	1362	12	0.9
2020-07-13	GGD Zeela	1946	58	3
2020-07-13	GGD Zuid-I	2503	13	0.5
2020-07-13	Veiligheids	3906	16	0.4
2020-07-20	Dienst Gez	2805	41	1.5
2020-07-20	GGD Amst	8234	166	2
2020-07-20	GGD Braba	4196	17	0.4
2020-07-20	GGD Drent	2524	5	0.2

2020-07-20GGD Flevo	2282	12	0.5
2020-07-20GGD Fryslâ	2648	5	0.2
2020-07-20GGD Gelde	4101	10	0.2
2020-07-20GGD Gooi	1863	16	0.9
2020-07-20GGD Groni	3030	8	0.3
2020-07-20GGD Haagl	7693	110	1.4
2020-07-20GGD Hart \	12996	62	0.5
2020-07-20GGD Holla	6974	88	1.3
2020-07-20GGD Holla	3284	35	1.1
2020-07-20GGD IJssell	3133	8	0.3
2020-07-20GGD Kenn	3723	36	1
2020-07-20GGD Limbu	2577	4	0.2
2020-07-20GGD Noor	4638	17	0.4
2020-07-20GGD Regio	2784	6	0.2
2020-07-20GGD Regio	12975	94	0.7
2020-07-20GGD Rotte	8042	296	3.7
2020-07-20GGD West	4335	108	2.5
2020-07-20GGD Zaans	1871	11	0.6
2020-07-20GGD Zeela	2879	43	1.5
2020-07-20GGD Zuid-I	3150	9	0.3
2020-07-20Veiligheids	5177	19	0.4
2020-07-27Dienst Gez	2601	55	2.1
2020-07-27GGD Amst	9121	455	5
2020-07-27GGD Braba	4068	61	1.5
2020-07-27GGD Drent	2043	10	0.5
2020-07-27GGD Flevo	2141	47	2.2
2020-07-27GGD Fryslâ	2419	7	0.3
2020-07-27GGD Gelde	3205	21	0.7
2020-07-27GGD Gooi	1750	38	2.2
2020-07-27GGD Groni	2952	19	0.6
2020-07-27GGD Haagl	8014	285	3.6
2020-07-27GGD Hart \	11272	130	1.2
2020-07-27GGD Holla	5894	112	1.9
2020-07-27GGD Holla	3401	25	0.7
2020-07-27GGD IJssell	2669	10	0.4
2020-07-27GGD Kenn	3478	62	1.8
2020-07-27GGD Limbu	1987	15	0.8
2020-07-27GGD Noor	3806	19	0.5
2020-07-27GGD Regio	2339	16	0.7
2020-07-27GGD Regio	10118	159	1.6
2020-07-27GGD Rotte	9065	639	7
2020-07-27GGD West	4533	181	4
2020-07-27GGD Zaans	1848	31	1.7
2020-07-27GGD Zeela	2195	40	1.8
2020-07-27GGD Zuid-I	2344	14	0.6

2020-07-27	Veiligheids	3844	25	0.7
2020-08-03	Dienst Gez	2135	87	4.1
2020-08-03	GGD Amst	11178	702	6.3
2020-08-03	GGD Braba	3431	54	1.6
2020-08-03	GGD Drent	2013	14	0.7
2020-08-03	GGD Flevo	1997	42	2.1
2020-08-03	GGD Fryslá	2168	31	1.4
2020-08-03	GGD Gelde	2876	42	1.5
2020-08-03	GGD Gooi	1678	32	1.9
2020-08-03	GGD Groni	2807	46	1.6
2020-08-03	GGD Haagl	6819	401	5.9
2020-08-03	GGD Hart	10212	228	2.2
2020-08-03	GGD Holla	4481	171	3.8
2020-08-03	GGD Holla	3087	49	1.6
2020-08-03	GGD IJssell	2431	31	1.3
2020-08-03	GGD Kenn	3228	69	2.1
2020-08-03	GGD Limbu	1986	46	2.3
2020-08-03	GGD Noor	3070	51	1.7
2020-08-03	GGD Regio	2353	25	1.1
2020-08-03	GGD Regio	9552	233	2.4
2020-08-03	GGD Rotte	9013	796	8.8
2020-08-03	GGD West	4262	274	6.4
2020-08-03	GGD Zaans	1655	49	3
2020-08-03	GGD Zeela	1688	26	1.5
2020-08-03	GGD Zuid-I	2332	31	1.3
2020-08-03	Veiligheids	3236	40	1.2
2020-08-10	Dienst Gez	2099	88	4.2
2020-08-10	GGD Amst	11428	709	6.2
2020-08-10	GGD Braba	4145	97	2.3
2020-08-10	GGD Drent	1946	13	0.7
2020-08-10	GGD Flevo	2079	58	2.8
2020-08-10	GGD Fryslá	3152	59	1.9
2020-08-10	GGD Gelde	3241	47	1.5
2020-08-10	GGD Gooi	1995	66	3.3
2020-08-10	GGD Groni	3580	58	1.6
2020-08-10	GGD Haagl	6923	422	6.1
2020-08-10	GGD Hart	10828	284	2.6
2020-08-10	GGD Holla	4429	145	3.3
2020-08-10	GGD Holla	3254	44	1.4
2020-08-10	GGD IJssell	2792	38	1.4
2020-08-10	GGD Kenn	3771	119	3.2
2020-08-10	GGD Limbu	2317	79	3.4
2020-08-10	GGD Noor	3215	46	1.4
2020-08-10	GGD Regio	2925	47	1.6
2020-08-10	GGD Regio	8771	234	2.7

2020-08-10GGD Rotte	7874	694	8.8
2020-08-10GGD West	3910	165	4.2
2020-08-10GGD Zaans	1905	49	2.6
2020-08-10GGD Zeela	1316	21	1.6
2020-08-10GGD Zuid-I	2643	38	1.4
2020-08-10Veiligheids	3332	58	1.7

GGD	Aantal getes	Aantal pos	Percentage	Aantal get	Aantal pos	Percentage	Verschil aa	Verschil aa	Percentuel
Dienst Gez	2135	87	4.1	2099	88	4.2	-36	1	-1.7
GGD Amst	11178	702	6.3	11428	709	6.2	250	7	2.2
GGD Braba	3431	54	1.6	4145	97	2.3	714	43	20.8
GGD Drent	2013	14	0.7	1946	13	0.7	-67	-1	-3.3
GGD Flevo	1997	42	2.1	2079	58	2.8	82	16	4.1
GGD Fryslá	2168	31	1.4	3152	59	1.9	984	28	45.4
GGD Gelde	2876	42	1.5	3241	47	1.5	365	5	12.7
GGD Gooi	1678	32	1.9	1995	66	3.3	317	34	18.9
GGD Groni	2807	46	1.6	3580	58	1.6	773	12	27.5
GGD Haagl	6819	401	5.9	6923	422	6.1	104	21	1.5
GGD Hart	10212	228	2.2	10828	284	2.6	616	56	6
GGD Holla	4481	171	3.8	4429	145	3.3	-52	-26	-1.2
GGD Holla	3087	49	1.6	3254	44	1.4	167	-5	5.4
GGD IJssel	2431	31	1.3	2792	38	1.4	361	7	14.8
GGD Kenn	3228	69	2.1	3771	119	3.2	543	50	16.8
GGD Limbu	1986	46	2.3	2317	79	3.4	331	33	16.7
GGD Noor	3070	51	1.7	3215	46	1.4	145	-5	4.7
GGD Regio	2353	25	1.1	2925	47	1.6	572	22	24.3
GGD Regio	9552	233	2.4	8771	234	2.7	-781	1	-8.2
GGD Rotte	9013	796	8.8	7874	694	8.8	-1139	-102	-12.6
GGD West	4262	274	6.4	3910	165	4.2	-352	-109	-8.3
GGD Zaans	1655	49	3	1905	49	2.6	250	0	15.1
GGD Zeela	1688	26	1.5	1316	21	1.6	-372	-5	-22
GGD Zuid-I	2332	31	1.3	2643	38	1.4	311	7	13.3
Veiligheids	3236	40	1.2	3332	58	1.7	96	18	3
Totaal	99688	3570	3.6	103870	3678	3.5	4182	108	4.2
Weeknum	32			33					

Percentuele stijging/daling aantal positief
1.1
1
79.6
-7.1
38.1
90.3
11.9
106.2
26.1
5.2
24.6
-15.2
-10.2
22.6
72.5
71.7
-9.8
88
0.4
-12.8
-39.8
0
-19.2
22.6
45
3

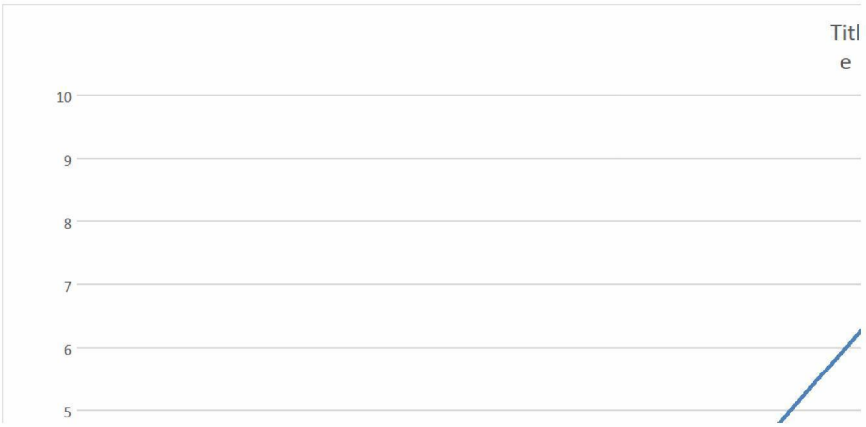
Months	(Multiple Items)					
Sum of Percentage positief	Column Labels					
Row Labels	1-jun	8-jun	15-jun	22-jun	29-jun	
Dienst Gezondheid & Jeugd ZHZ	3.7	1.2	0.7	0.5	0.2	
GGD Amsterdam	2.4	1.9	1.2	1.2	0.7	
GGD Brabant-Zuidoost	2	1.6	0.7	0.3	0.4	
GGD Drenthe	0.7	0.4	0.2	0.1	0.1	
GGD Flevoland	1.2	1	0.6	0.6	0.1	
GGD Fryslân	0.5	1.1	0.1	0.1	0.3	
GGD Gelderland-Zuid	3.4	0.8	0.5	0.8	0.3	
GGD Gooi en Vechtstreek	0.1	1.1	0.8	2.1	1.6	
GGD Groningen	0.1	0.4	0.1	0	0.1	
GGD Haaglanden	3	2.7	1.5	1.3	0.8	
GGD Hart voor Brabant	2.2	1.4	1.1	0.8	0.8	
GGD Hollands-Midden	1.9	1.8	1	0.4	0.5	
GGD Hollands-Noorden	0.6	0.3	0.2	0.2	0.1	
GGD IJsselland	1.2	1.2	0.8	0.5	0.6	
GGD Kennemerland	1.4	0.9	0.5	0.2	0.5	
GGD Limburg-Noord	1.3	1.5	0.5	0.1	0.1	
GGD Noord- en Oost-Gelderland	3.2	2	1.7	0.9	0.3	
GGD Regio Twente	0.6	0.5	0.5	0.3	0.5	
GGD Regio Utrecht	2.2	1.4	1	0.9	0.5	
GGD Rotterdam-Rijnmond	3.4	2.5	1.8	1.6	1.5	
GGD West-Brabant	2.1	0.7	0.5	0.3	0.6	
GGD Zaanstreek/Waterland	1.3	2.2	1.2	0.2	0.3	
GGD Zeeland	0.6	0.2	0.4	0.2	0.3	
GGD Zuid-Limburg	1.3	0.8	0.3	0.2	0.6	
Veiligheids- en Gezondheidsregio Gelderland-Midden	1.8	1.3	1.1	0.3	0.3	

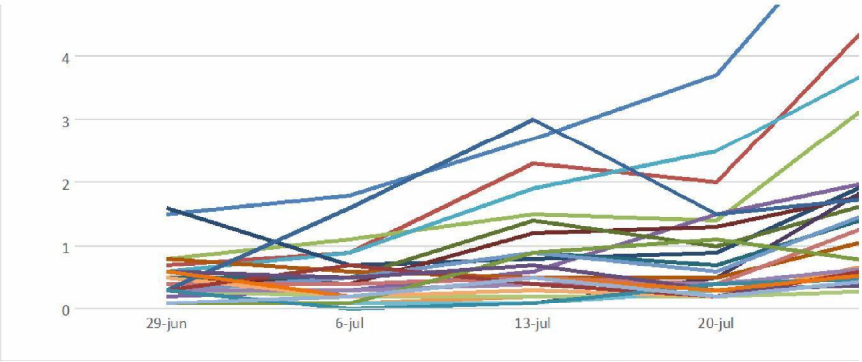
6-jul	13-jul	20-jul	27-jul	3-aug	10-aug
0.3	0.6	1.5	2.1	4.1	4.2
0.9	2.3	2	5	6.3	6.2
0.4	0.5	0.4	1.5	1.6	2.3
0.2	0.5	0.2	0.5	0.7	0.7
0.1	0.1	0.5	2.2	2.1	2.8
0.2	0.2	0.2	0.3	1.4	1.9
0.7	0.4	0.2	0.7	1.5	1.5
0.7	0.8	0.9	2.2	1.9	3.3
0.1	0.1	0.3	0.6	1.6	1.6
1.1	1.5	1.4	3.6	5.9	6.1
0.6	0.5	0.5	1.2	2.2	2.6
0.4	1.2	1.3	1.9	3.8	3.3
0.1	0.9	1.1	0.7	1.6	1.4
0.5	0.7	0.3	0.4	1.3	1.4
0.5	1.4	1	1.8	2.1	3.2
0.1	0.2	0.2	0.8	2.3	3.4
0	0.1	0.4	0.5	1.7	1.4
0.2	0.3	0.2	0.7	1.1	1.6
0.5	0.9	0.7	1.6	2.4	2.7
1.8	2.7	3.7	7	8.8	8.8
0.9	1.9	2.5	4	6.4	4.2
0.5	0.9	0.6	1.7	3	2.6
1.6	3	1.5	1.8	1.5	1.6
0.2	0.5	0.3	0.6	1.3	1.4
0.3	0.4	0.4	0.7	1.2	1.7

Months	(Multiple Items)				
Sum of Aantal getest	Column Labels				
Row Labels	1-jun	8-jun	15-jun	22-jun	29-jun
Dienst Gezondheid & Jeugd ZHZ	1477	1478	1333	1655	2016
GGD Amsterdam	4402	4798	4998	4264	4433
GGD Brabant-Zuidoost	1809	2517	3047	2820	2553
GGD Drenthe	991	1130	1403	1461	1653
GGD Flevoland	1271	1449	1439	1508	1580
GGD Fryslân	1067	1405	1347	1518	1814
GGD Gelderland-Zuid	2249	2090	2066	2050	2382
GGD Gooi en Vechtstreek	910	994	1192	1179	1256
GGD Groningen	1007	1163	1482	1479	1834
GGD Haaglanden	3335	4118	4568	4641	5043
GGD Hart voor Brabant	6418	7642	8244	7238	7808
GGD Hollands-Midden	2287	3389	3874	3917	3996
GGD Hollands-Noorden	1401	1561	1666	1889	1978
GGD IJsselland	1415	1625	1829	1947	2081
GGD Kennemerland	1351	1701	2110	2142	2190
GGD Limburg-Noord	1496	1473	1478	1551	1666
GGD Noord- en Oost-Gelderland	1947	1999	2182	2427	3000
GGD Regio Twente	1222	1397	1721	1497	1594
GGD Regio Utrecht	5008	5609	5914	6063	6930
GGD Rotterdam-Rijnmond	2985	4637	4820	4409	5200
GGD West-Brabant	2059	2391	2545	2376	2703
GGD Zaanstreek/Waterland	1034	1011	1208	1084	1113
GGD Zeeland	669	824	705	944	1257
GGD Zuid-Limburg	2034	1906	1832	1846	1987
Veiligheids- en Gezondheidsregio Gelderland-Midden	2177	2527	2723	2936	3085
Grand Total	52021	60834	65726	64841	71152

6-jul	13-jul	20-jul	27-jul	3-aug	10-aug	Grand Total
2242	2643	2805	2601	2135	2099	22484
4879	5654	8234	9121	11178	11428	73389
3083	3571	4196	4068	3431	4145	35240
1659	1904	2524	2043	2013	1946	18727
1621	1749	2282	2141	1997	2079	19116
1919	2098	2648	2419	2168	3152	21555
2726	3402	4101	3205	2876	3241	30388
1345	1457	1863	1750	1678	1995	15619
2082	2374	3030	2952	2807	3580	23790
5570	6707	7693	8014	6819	6923	63431
8606	10596	12996	11272	10212	10828	101860
4271	5213	6974	5894	4481	4429	48725
2109	2567	3284	3401	3087	3254	26197
2201	2403	3133	2669	2431	2792	24526
2301	2425	3723	3478	3228	3771	28420
1623	1990	2577	1987	1986	2317	20144
3220	3744	4638	3806	3070	3215	33248
2071	2375	2784	2339	2353	2925	22278
8590	10838	12975	10118	9552	8771	90368
5843	6715	8042	9065	9013	7874	68603
3064	3664	4335	4533	4262	3910	35842
1284	1362	1871	1848	1655	1905	15375
1471	1946	2879	2195	1688	1316	15894
2155	2503	3150	2344	2332	2643	24732
3287	3906	5177	3844	3236	3332	36230
79222	93806	117914	107107	99688	103870	916181

GGD	29-jun	6-jul	13-jul	20-jul	27-jul	3-aug	10-aug
GGD Rotterdam-Rijnmor	1.5	1.8	2.7	3.7	7	8.8	8.8
GGD Amsterdam	0.7	0.9	2.3	2	5	6.3	6.2
GGD Haaglanden	0.8	1.1	1.5	1.4	3.6	5.9	6.1
Dienst Gezondheid & Jeu	0.2	0.3	0.6	1.5	2.1	4.1	4.2
GGD West-Brabant	0.6	0.9	1.9	2.5	4	6.4	4.2
GGD Limburg-Noord	0.1	0.1	0.2	0.2	0.8	2.3	3.4
GGD Gooi en Vechtstree	1.6	0.7	0.8	0.9	2.2	1.9	3.3
GGD Hollands-Midden	0.5	0.4	1.2	1.3	1.9	3.8	3.3
GGD Kennemerland	0.5	0.5	1.4	1	1.8	2.1	3.2
GGD Flevoland	0.1	0.1	0.1	0.5	2.2	2.1	2.8
GGD Regio Utrecht	0.5	0.5	0.9	0.7	1.6	2.4	2.7
GGD Hart voor Brabant	0.8	0.6	0.5	0.5	1.2	2.2	2.6
GGD Zaanstreek/Waterla	0.3	0.5	0.9	0.6	1.7	3	2.6
GGD Brabant-Zuidoost	0.4	0.4	0.5	0.4	1.5	1.6	2.3
GGD Fryslân	0.3	0.2	0.2	0.2	0.3	1.4	1.9
Veiligheids- en Gezondhe	0.3	0.3	0.4	0.4	0.7	1.2	1.7
GGD Groningen	0.1	0.1	0.1	0.3	0.6	1.6	1.6
GGD Regio Twente	0.5	0.2	0.3	0.2	0.7	1.1	1.6
GGD Zeeland	0.3	1.6	3	1.5	1.8	1.5	1.6
GGD Gelderland-Zuid	0.3	0.7	0.4	0.2	0.7	1.5	1.5
GGD Hollands-Noorden	0.1	0.1	0.9	1.1	0.7	1.6	1.4
GGD IJsselland	0.6	0.5	0.7	0.3	0.4	1.3	1.4
GGD Noord- en Oost-Gel	0.3	0	0.1	0.4	0.5	1.7	1.4
GGD Zuid-Limburg	0.6	0.2	0.5	0.3	0.6	1.3	1.4
GGD Drenthe	0.1	0.2	0.5	0.2	0.5	0.7	0.7

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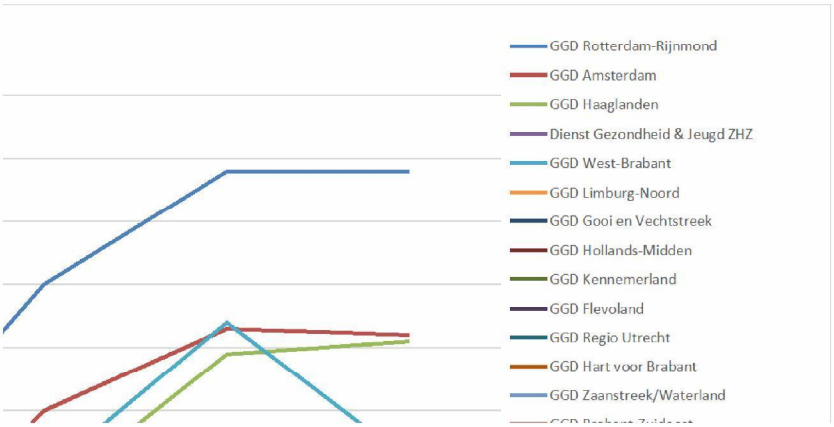
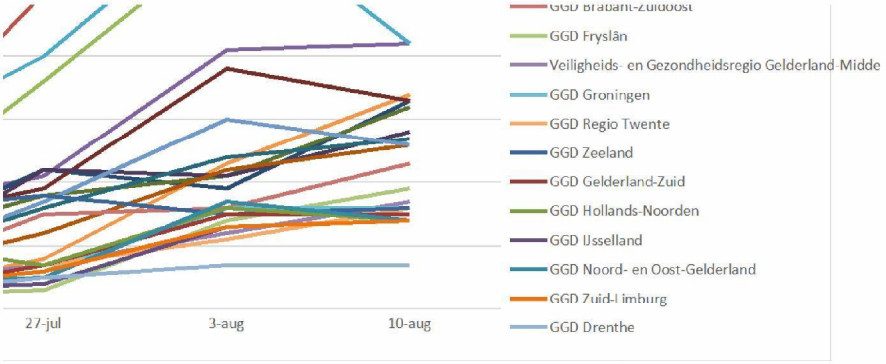
GGD Rotterdam-Rijnmond	5200	5843	6715	8042	9065	9013	7874
GGD Amsterdam	4433	4879	5654	8234	9121	11178	11428
GGD Haaglanden	5043	5570	6707	7693	8014	6819	6923
Dienst Gezondheid & Jeugd	2016	2242	2643	2805	2601	2135	2099
GGD West-Brabant	2703	3064	3664	4335	4533	4262	3910
GGD Limburg-Noord	1666	1623	1990	2577	1987	1986	2317
GGD Gooi en Vechtstreek	1256	1345	1457	1863	1750	1678	1995
GGD Hollands-Midden	3996	4271	5213	6974	5894	4481	4429
GGD Kennemerland	2190	2301	2425	3723	3478	3228	3771
GGD Flevoland	1580	1621	1749	2282	2141	1997	2079
GGD Regio Utrecht	6930	8590	10838	12975	10118	9552	8771
GGD Hart voor Brabant	7808	8606	10596	12996	11272	10212	10828
GGD Zaanstreek/Waterland	1113	1284	1362	1871	1848	1655	1905
GGD Brabant-Zuidoost	2553	3083	3571	4196	4068	3431	4145
GGD Fryslân	1814	1919	2098	2648	2419	2168	3152
Veiligheids- en Gezondheid	3085	3287	3906	5177	3844	3236	3332
GGD Groningen	1834	2082	2374	3030	2952	2807	3580
GGD Regio Twente	1594	2071	2375	2784	2339	2353	2925
GGD Zeeland	1257	1471	1946	2879	2195	1688	1316
GGD Gelderland-Zuid	2382	2726	3402	4101	3205	2876	3241
GGD Hollands-Noorden	1978	2109	2567	3284	3401	3087	3254
GGD IJsselland	2081	2201	2403	3133	2669	2431	2792
GGD Noord- en Oost-Gelde	3000	3220	3744	4638	3806	3070	3215
GGD Zuid-Limburg	1987	2155	2503	3150	2344	2332	2643
GGD Drenthe	1653	1659	1904	2524	2043	2013	1946

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GGD Hollands-Noorden
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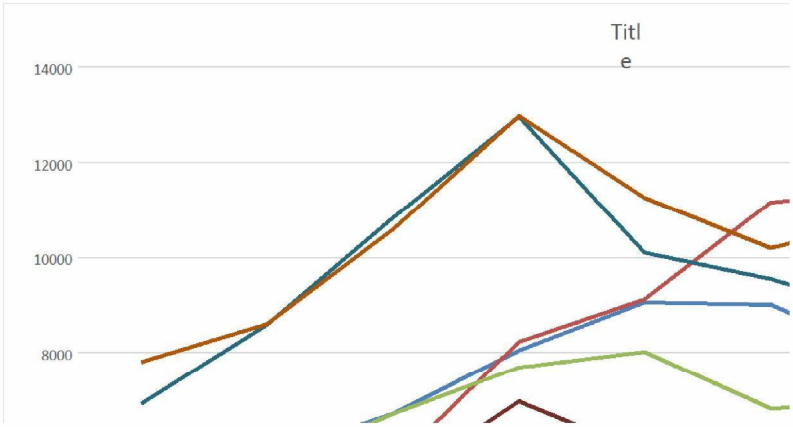
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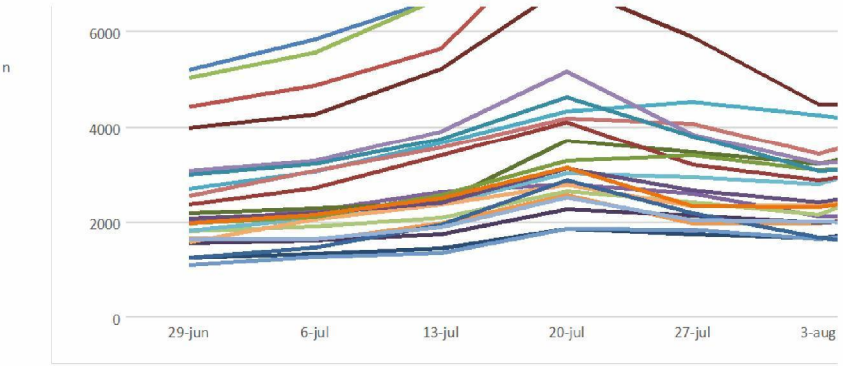
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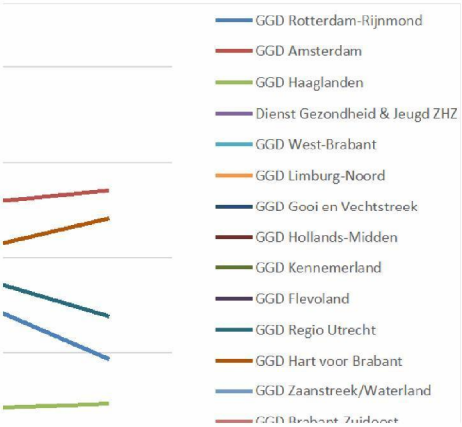
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GGD Limburg-Noord
GGD Gooi en Vechtstreek
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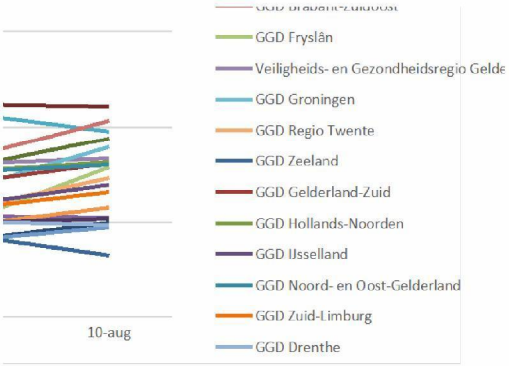
GGD Kennemerland
GGD Flevoland
GGD Regio Utrecht
GGD Hart voor Brabant
GGD Zaanstreek/Waterland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GGD IJsselland
GGD Noord- en Oost-Gelderland
GGD Zuid-Limburg
GGD Drenthe
10-aug

National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

The National Immunisation Programme in the Netherlands

Surveillance and developments in 2019-2020

RIVM Report 2020-0077

RIVM Report 2020-0077

Colophon

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Contents

Synopsis

The National Immunisation Programme in the Netherlands
Surveillance and developments in 2019-2020

In 2019 1,520,301 persons (children and pregnant women) were vaccinated under the National Immunisation Programme (NIP). These persons received 2,929,264 vaccinations in total. The national immunisation coverage has slightly increased for the first time in five years.

As in previous years, the number of notified cases in 2019 was low for *Haemophilus influenzae* type b (Hib, 39), diphtheria (0), tetanus (0), rubella (0), and polio (0). The number of measles cases in 2019 was relatively high with 84 reported cases. The number of mumps cases was low (131), but double than that of the previous year. The number of notifications of pertussis (...) and hepatitis B (1205) remained stable. The overall number of meningococcal disease (159) decreased after an increase from 2015 to 2018 (90 to 206).
In 2020 following implementation of Dutch COVID-19 response measures, the reported incidence of pertussis, invasive pneumococcal disease (IPD), invasive meningococcal disease (IMD), and mumps has decreased.

The estimated effectiveness of maternal pertussis vaccination in preventing pertussis in 0-3-month-olds was 73-90% in 2019, assuming a 20-40% vaccination coverage, and 93-97% in 2020, taking into account 50-70% coverage.
A study on the early effects of HPV vaccination on cervical lesions in opportunistic screening, found that fully vaccinated women (12-24 years of age) had a lower risk for an high-risk HPV infection (0.68; 95%CI 0.62-0.74), borderline (pre)neoplastic changes or worse (0.77; 0.73-0.82) and moderate to severe dysplasia or worse (0.45; 0.37-0.56) than unvaccinated women of the same age.

In 2020, PPV23 vaccination was to be offered to all 60-, 65-, 70- and 75-year-olds in the Netherlands. However, due to the COVID-19 pandemic, priority has been given to the oldest age groups, meaning that in Autumn 2020 all 73-79-year-olds will be offered PPV23 vaccination.
In 2020, the Health Council of the Netherlands issued a positive recommendation to add vaccination against varicella in the NIP in the Caribbean Netherlands and not in the European Netherlands. The council also recommends that residents of these islands who have not yet had an infection be offered a one-off vaccination against VZV.

Keywords: National Immunisation Programme (NIP), diphtheria, Haemophilus influenzae, hepatitis B, human papillomavirus (HPV), measles, meningococcal disease, mumps, pertussis, pneumococcal disease, poliomyelitis, rubella, tetanus, hepatitis A, respiratory syncytial virus (RSV), rotavirus, Varicella zoster virus (VZV)

Publiekssamenvatting

Het Rijksvaccinatieprogramma in Nederland
Surveillance en ontwikkelingen in 2019-2020

In 2018 zijn 1.520.301 personen (kinderen en zwangeren) gevaccineerd via het
Rijksvaccinatieprogramma (RVP). In totaal ontvingen zij 2.929.264 vaccinaties. De landelijke vaccinatiegraad is voor het eerst sinds 5 jaar licht gestegen.

Net als in voorgaande jaren waren er in 2019 weinig meldingen van *Haemophilus influenzae* type b (Hib; 39), difterie (0), tetanus (0), rodehond (0) en polio (0). Het aantal meldingen van mazelen was met 84 relatief hoog. Het aantal meldingen van bof was laag (131), maar verdubbeld ten opzichte van het voorgaande jaar. Het aantal meldingen van kinkhoest (...) en hepatitis B (1205) bleef stabiel. Het totale aantal meldingen van meningokokkenziekte (159) daalde na een stijging van 2015 tot 2018 (90 tot 206).
In 2020 na de implementatie van de COVID-19 maatregelen is de gerapporteerde incidentie van kinkhoest, invasieve pneumokokkenziekte, invasieve meningokokkenziekte en bof gedaald.

De geschatte effectiviteit van maternale kinkhoestvaccinatie in het voorkomen van kinkhoest bij kinderen 0-3 maanden oud was 73-90%, uitgaande van een vaccinatiegraad van 20-40% in 2019 en 93-97% in 2020, rekening houdend met een vaccinatiegraad van 50-70%.
In een studie naar de vroege effecten van HPV vaccinatie op cervicale laesies in opportunistische screening, hadden volledig gevaccineerde vrouwen (12-24 jaar) een lager risico op een hoog-risico HPV infectie (0,68; 95%BI 0,62-0,74), borderline (pre)neoplastische veranderingen of erger (0,77; 0,73-0,82) en matig tot ernstige dysplasie of erger (0,45; 0,37-0,56) dan ongevaccineerde vrouwen van dezelfde leeftijd.

In 2020 zou PPV23-vaccinatie worden aangeboden aan alle 60-, 65-, 70- en 75-jarigen in Nederland. Vanwege de COVID-19-pandemie is echter prioriteit gegeven aan de oudste leeftijdsgroepen, wat betekent dat in het najaar van 2020 alle 73-79-jarigen PPV23-vaccinatie aangeboden zullen krijgen.
In 2020 heeft de Gezondheidsraad geadviseerd om vaccinatie tegen waterpokken in Caribisch Nederland wel toe te voegen aan het RVP en in Europees Nederland niet. De Gezondheidsraad adviseert ook om bewoners van deze eilanden die nog geen infectie hebben gehad een eenmalige vaccinatie tegen VZV aan te bieden.

Kernwoorden: Rijksvaccinatieprogramma (RVP), difterie, Haemophilus influenzae, hepatitis B, humaan papillomavirus (HPV), mazelen, meningokokkenziekte, bof, kinkhoest, pneumokokkenziekte, polio, rodehond, tetanus, hepatitis A, respiratoir syncytieel virus (RSV), rotavirus, Varicella zoster virus (VZV)

Infographic

Preface

This report presents an overview of surveillance and developments 2019 and the first part of 2020 that are relevant for the Netherlands with respect to diseases included in the current National Immunisation Programme (NIP): diphtheria, *Haemophilus influenzae* serotype b (Hib) disease, hepatitis B, human papillomavirus (HPV) infection, measles, meningococcal disease, mumps, pertussis, pneumococcal disease, poliomyelitis, rubella, and tetanus. It also describes surveillance data concerning potential target diseases: hepatitis A, respiratory syncytial virus (RSV), rotavirus, and Varicella zoster virus (VZV) infection. In addition, it includes an overview of vaccines for infectious diseases undergoing clinical trials that are relevant for the Netherlands, including COVID19 vaccines.

The report is structured as follows:
Chapter 1 contains a summary introduction of the NIP organisation, new recommendations from the Health Council of the Netherlands, and new decisions issued by the Ministry of Health, Welfare and Sports. Recent data regarding vaccination coverage are discussed in Chapter 2. Chapter 3 focuses on the burden of diseases included in the NIP. Public acceptance of vaccination and NIP communication are described in Chapter 4, whilst information on adverse events following immunisation (AEFI) is given in Chapter 5. Chapter 6 presents various research topics that address the evaluation of the NIP in a broader sense. Chapter 7 focuses on current NIP target diseases. For each disease, the section starts with key points outlining the most prominent findings followed by figures and tables. An update of information on epidemiology, the pathogen, the outcome of current and ongoing studies, and international developments is then provided. Vaccination coverage and developments in the current NIP target diseases in the Dutch overseas territories, including the Dutch Caribbean islands, are presented in Chapter 8. Chapter 9 describes potential new target diseases that are under consideration for (future) vaccination. Finally, Chapter 10 provides an overview of vaccines for infectious diseases that are undergoing clinical trials and are potentially relevant for the Netherlands.

Appendix 1 describes the surveillance methods used to monitor the NIP. Appendix 2 reports on mortality and morbidity figures from 1997 onwards based on various data sources. Appendix 3 contains an overview of changes in the NIP since 2000, whilst Appendix 4 presents the composition of the vaccines used in the period 2019-2020. Appendix 5 gives an overview of recent publications by the National Institute for Public Health and the Environment (RIVM), and Appendix 6 lists relevant websites.

Comprehensive summary

The current National Immunisation Programme (NIP) includes vaccination against 12 vaccine-preventable diseases (VPDs), i.e. diphtheria, pertussis, tetanus, poliomyelitis, *Haemophilus influenzae* disease, measles, mumps, rubella, meningococcal disease, hepatitis B, pneumococcal disease, and human papillomavirus (HPV) infection (girls) (Figure 1). This report presents surveillance data and scientific developments relevant for the Netherlands with regard to these diseases as well as for (potential) new target diseases, i.e. rotavirus infection, Varicella zoster virus (VZV) infection (varicella and herpes zoster), hepatitis A, and respiratory syncytial virus (RSV) infection.

Current vaccination schedule

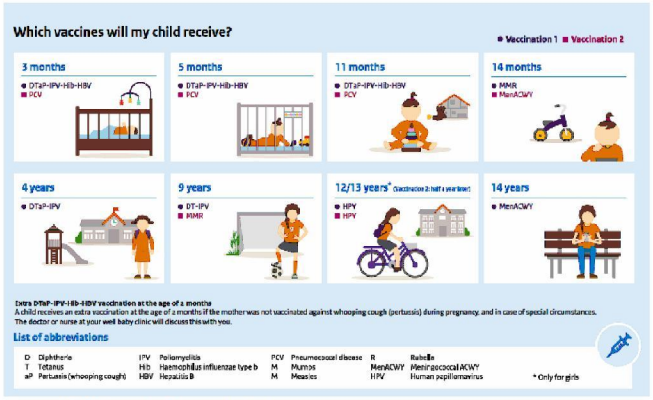


Figure 1 NIP vaccination schedule
Source:
http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/Professionals

Vaccination coverage

The national immunisation coverage has slightly increased for the first time in five years. In infants born in 2017, this applies in particular to the mumps, measles and rubella (MMR) vaccination. This rose by 0.7% to 93.6%. The national immunisation coverage for HPV vaccination (cervical cancer) for girls, born in 2005, has increased by 7.5% to 53%. The provisional national vaccination coverage for the meningococcal ACWY vaccination for adolescents born in 2001-2005 is high (86%). It is reassuring that the effect of the COVID-19 pandemic on participation in the first MMR vaccination seems limited, despite some vaccination delay.

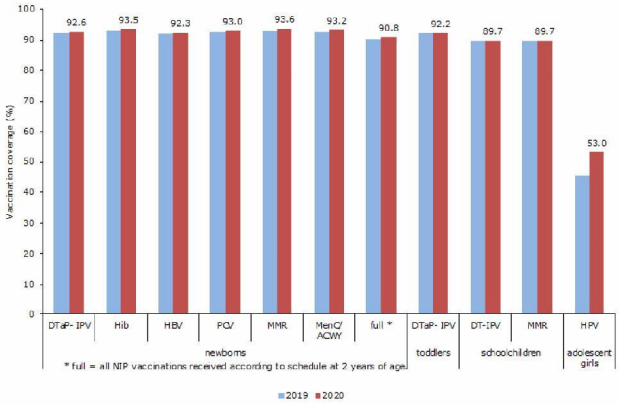


Figure 2 Vaccination coverage per vaccine for newborns, toddlers, schoolchildren and adolescent girls in 2019 and 2020
Source: Præventis

Acceptance of vaccination

Several quantitative and qualitative studies showed it is important to direct communication strategies and materials regarding vaccines at the target groups. For example, communication regarding the MenACWY vaccination should focus on both the teenagers and parents. Furthermore, including the relevant health care workers in this communication process is important. Research regarding the maternal pertussis vaccination (MPV) showed that the health care workers (i.e. midwives, gynaecologists) are the preferred source of information to women, regardless of them having heard or read about MPV already. Therefore, information should be tailored and consultation for target group could increase vaccine acceptance. These strategies should be implemented before mandates are enforced as the latter have shown to not necessarily be effective in increasing vaccine acceptance.

Burden of disease

For the year 2019, the estimated burden of disease caused by (partially) vaccine-preventable diseases, as expressed in Disability Adjusted Life Years (DALYs), was highest for HPV (19,400 DALYs (75% among women)), invasive pneumococcal disease (9,500 DALYs/year), pertussis (2,600 DALYs/year), rotavirus infection (1,100 DALYs/year), invasive *Haemophilus influenzae* disease (970 DALYs/year), and invasive meningococcal disease (890 DALYs/year). For most diseases, the estimated burden in 2019 was comparable to the estimated burden in 2018. The disease burden of invasive pneumococcal and meningococcal disease was lower in 2019, whereas the burden of HPV (for females), measles and pertussis was somewhat higher in 2019 than in 2018.

Adverse events

In 2019, Lareb received 2,009 notifications representing a total of 7,378 adverse events following immunisation (AEFI). Compared to 2018, the number of reports increased by 32%, while the number of reported AEFIs increased by 42%. The increase in number of reports is mainly due to the catch-up campaign of MenACWY vaccination in adolescents. The number of reported AEFIs per report remained stable (3.7).
No new signals of disturbing adverse events were found.

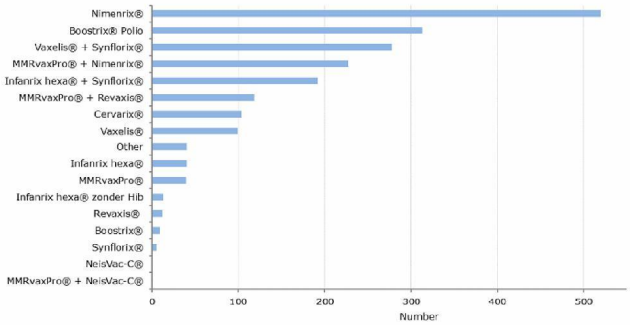


Figure 3 Number of reports of adverse events per suspected vaccine(s) in 2019
Source: Lareb

NIP-wide research topics

Following implementation of Dutch COVID-19 response measures, the reported incidence of pertussis, invasive pneumococcal disease (IPD), invasive meningococcal disease (IMD), and mumps has decreased.

Current NIP

Diphtheria

In 2019, one possible diphtheria case was reported with unknown vaccination history. Although clinical signs were very suspicious for diphtheria and patient received diphtheria antitoxin as treatment, no Corynebacterium was found. In 2020, until June 1st, no diphtheria cases were notified.
A European serosurveillance study showed that a substantial part of 40-60-year-olds had non-protective DT levels. Levels <0.01 IU/ml varied between 4% and 43%. For 0.1 IU/ml, these percentages varied from 23% up to around 80%. The percentage unprotected in the Netherlands was 12.8% (<0.01 IU/ml) and 57.5% (<0.1 IU/ml).

Haemophilus influenzae disease

In 2019, the number of cases of *Haemophilus influenzae* type b (Hib) disease was similar to 2018 (39 vs 43 cases). Up to May 2020, 16 Hib cases have been reported, somewhat more than in the same period in 2019 (n=10) but similar to 2018 (n=17). In 2019, the incidence of Hib disease was highest among children under 5 years old (2.0 per 100,000). After an increasing trend in incidence observed from 2011 to 2016, the incidence stabilized in the period 2017-2019. There were 19 Hib cases in vaccine-eligible children in 2019, of which nine were

sufficiently vaccinated, resulting in a Hib vaccine effectiveness estimate of 93%, similar to previous years. In 2019, a similar number of cases of non-typable Hi (NTHi) disease were reported as in 2018 (165 vs. 167), suggesting a stabilization of NTHi disease. No rise was observed in Hi due to other serotypes.

Hepatitis B

The incidence of acute hepatitis B reports (n=104) remained stable at 0.6 per 100,000 population in 2019. Sexual contact was the most frequently reported risk factor for acute HBV infection, but the route of transmission remained unknown for a third of cases. No cases of acute hepatitis B were reported among children born after the introduction of universal HBV vaccination in 2011. In 2019, genotype A continued to be the dominant genotype among acute HBV cases with 58% of 74 genotyped cases.
The number of newly diagnosed chronic HBV infections was 1,205 in 2019, corresponding to an incidence of 6.2 per 100,000.

Human papillomavirus (HPV) infection

The incidence of cervical cancer has been increasing in 2019 up to 9.90 per 100,000, while the number of deaths caused by cervical cancer has remained relatively stable. The incidence of other HPV-related cancers was stable as well. In a prospective cohort study (HAVANA), high vaccine effectiveness (VE) against vaccine types HPV16/18 was found for persistent cervicovaginal infections up to nine years post-vaccination. This is also reflected in more clinically relevant findings: A study on the early effects of HPV vaccination on cervical lesions in opportunistic screening, found that fully vaccinated women (12-24 years of age) had a lower risk for hrHPV, ASC-US or worse and (H)SIL or worse. Moreover, using GP data from sentinel surveillance systems, it was shown that the bivalent HPV vaccine also provides partial protection against GW. Regarding seroprevalence data, type-specific HPV-seroprevalence increases were noted in unvaccinated women between 2006-07 and 2016-17 (Pienter studies). In men, overall HPV seroprevalence remained stable in the same period.

Measles

The number of measles cases in 2019 was relatively high with 84 notified cases. However, in the first six months of 2020 only 2 cases were reported. From June to August 2019 a local outbreak occurred in a low vaccination municipality with 32 reported cases, mainly among unvaccinated children. Genotype D8 was the only genotype detected. Preliminary analyses of the population-based serosurvey (PIENTER study) conducted in 2016/2017 indicate high overall seroprevalence of protective antibodies in the Dutch population of 97% for measles.

Meningococcal disease

In 2019, the overall incidence of meningococcal disease decreased after an increase from 2015 to 2018. In April to June 2020, the number of cases was 80% lower than in the same period in the last five years, which may be (partly) related to the COVID-19 measures that were in place during these months, including social distancing and school closures. The number of cases with meningococcal serogroup C disease is still very low, with six cases reported in 2019.

The vaccination uptake of the MenACWY vaccination campaign in 2018/2019 among 14-18 year olds was 84% and an additional 2% of the eligible population got vaccinated prior to the campaign. A lower uptake was observed when parents were born abroad, especially for parents born in Morocco or Turkey.
In 2019, the incidence of meningococcal serogroup W (MenW) disease decreased to 0.39 per 100,000 (n=62), after an increase in the number of cases from 2015 to 2018. In the first six months of 2020, only eight cases have been reported with no cases reported in April to June. The decrease of MenW in 2019 and the first months of 2020 was observed in vaccinated as well as unvaccinated age groups. Among children eligible for MenACWY vaccination at 14 months, there has been one vaccinated and one unvaccinated MenW case. Among adolescents eligible for MenACWY vaccination, there have been no MenW cases.
The incidence of meningococcal serogroup B (MenB) disease has been declining steadily since the late nineties and has stabilised at an incidence of 0.5 per 100,000 since 2011. In 2019, 72 cases and five deaths of MenB disease were reported, which was similar to 2018 (74 cases and five deaths). The incidence of MenB disease was highest in children aged under 5 years, with 22 cases in 2018 (2.5 per 100,000). The number of cases of meningococcal disease caused by serogroup Y or other serogroups is low and stable.

Mumps

The incidence of mumps in 2019 was low (0.8 per 100,000 population; n=131) but doubled compared to the year before. The increase in cases continued in the first quarter of 2020 but stopped abruptly in the second quarter of 2020. Most of the mumps cases in the Netherlands were caused by mumps virus genotype G.

Pertussis

In 2019, the overall incidence rate (IR) of pertussis notifications was 36.8 per 100,000 compared with 28.4 per 100,000 in 2018. In 2020 up to April 1st, the IR was 16.6 per 100,000; this IR was probably affected by the control measures in view of the covid-19 pandemic.
In April and May 2020, vaccination coverage of the maternal pertussis vaccination was estimated to be about 70%. In 2019, estimates for the effectiveness of the maternal pertussis vaccination in preventing pertussis in 0-3-month-olds was 73%-90%s , assuming a 20%-40% vaccination coverage. For 2020, the VE amounted to 93%-97%, taking into account 50%-70% coverage.
The prevalence of prn-deficient strains in the Netherlands sharply increased in 2018-2020.

Pneumococcal disease

In April and May 2020, the number of IPD dropped by 80% compared with the 5-year average, most likely related to COVID-19 measures. This influenced the overall and age-specific incidence and time trends of IPD in 2019/2020. In epidemiological year 2019/2020 (June to May), 43 children <5 years of age with IPD were reported, of which only one case was caused by a serotype included in the 10-valent PCV.
In children <5 years of age, introduction of pneumococcal conjugate vaccination (PCV) in 2006 led to a large reduction of IPD. Since 2013/2014, however, the IPD incidence in children <5 years of age has

been increasing slightly due to a slow increase of IPD caused by serotypes not covered by the 10-valent PCV. In other age groups, similar trends were observed with very low incidence of IPD caused by vaccine serotypes and increasing incidence of IPD due to non-vaccine serotypes, compromising the overall impact of PCV implementation. Vaccine effectiveness (VE) of at least two doses of PCV10 was 89% (95%CI 72-96%) against vaccine type IPD. In 2020, PPV23 vaccination was to be offered to all 60-, 65-, 70- and 75-year-olds in the Netherlands. However, due to the COVID-19 pandemic, priority has been given to the oldest age groups, meaning that in Autumn 2020 all 73-79 year olds will be offered PPV23 vaccination.

Poliomyelitis

In 2019 and 2020 up to July 1st, no cases of poliomyelitis were reported in the Netherlands, including the Caribbean Netherlands.
In an historic announcement on World Polio Day (24 October 2019), an independent commission of experts concluded that wild poliovirus type 3 (WPV3) has been eradicated worldwide. Two of three wildtype polioviruses (i.e. WPV2 and WPV3) have been declared eradicated.
In 2019-2020, poliovirus remained endemic in three countries; Nigeria, Afghanistan and Pakistan. On 21 Augustus 2019 Nigeria, and thus the Afro region, was free of wildtype poliovirus for 3 consecutive years. The certification process to declare the 5th of 6 WHO regions wildtype polio free is in progress and will likely be finalized in 2020. Worldwide, the number of circulating vaccine derived poliovirus (cVDPV) was higher in 2019 (368) than in 2018 (105). To sustain a world free of all polioviruses, the Global Polio Eradication Initiative (GPEI) has released a Polio Endgame Strategy 2019-2023 in 2019.

Rubella

In 2019, no rubella cases were notified. Preliminary analyses of the population-based serosurvey (PIENTER study) conducted in 2016/2017 indicate high overall seroprevalence of protective antibodies in the Dutch population of 95% for rubella. The highest susceptibility in the PIENTER study was seen among children within the orthodox Protestant community, born after the last rubella epidemic in 2005, indicating an outbreak can be expected after introduction of rubella virus in this community.

Tetanus

In 2019, no cases of tetanus were notified. In 2020, up to June 1st, two cases were reported, one elderly women who was not eligible for routine vaccination and one unvaccinated 12-year-old.
In a European seroprevalence study among 40-59-year-olds, seroprotection levels for tetanus were sufficient with only very few sera lacking basic immunity. In the Dutch serum samples, based on Pienter 3 participants, only 0.3% and 5.2% had anti-tetanus antibody levels <0.01 IU/ml and <0.1 IU/ml, respectively.

The immunisation programme in the Caribbean Netherlands

In general, vaccination coverage in the Dutch overseas territories, including Caribbean Netherlands (i.e., Bonaire, St. Eustatius and Saba) is high. In 2019, no vaccine preventable diseases were reported on Bonaire and Saba.

Findings from the Health Study Caribbean Netherlands indicate that HPV seroprevalence was high among individuals aged ≥15 years (34%), with over half of them being seropositive for ≥2 high-risk HPV types. Seroprevalence was substantial higher in women (51%) than men (18%), predominantly peaking in women aged 20-59 years. These data corroborate the decision regarding introduction of a sex-neutral HPV-vaccination program and the relevance for considering a population-based cervical cancer screening program in Caribbean Netherlands.

Potential NIP target diseases

Hepatitis A

In 2019, the number of reported hepatitis A cases (n=164) slightly decreased compared to 2018 (n=188), but remains higher compared to 2011-2016 (80-125 cases). No cases related to the MSM outbreak in 2016-2018 were seen in 2019. However, two new strains caused outbreaks among men who have sex with men (MSM). About two-third of the reported cases in 2019 is 20 years or older. Forty-one per cent of the Dutch cases were reported to be travel-related, with Morocco reported most frequently.

Respiratory syncytial virus (RSV) infection

A total of 95 RS-viruses (6,4%) were detected in 1493 combined nose swabs and throat swabs of patients with an acute respiratory infection (ARI), collected by sentinel GPs in the 2019/2020 respiratory season, compared with 12% in 2018/2019, 6% in 2017/2018 and 12% in 2016/2017. Due to the Covid-19 pandemic, more samples were collected with different age distribution than previous seasons in weeks 10-20, possibly partly explaining the relatively low RSV percentage.

Rotavirus infection

In 2019, 1,056 detected cases of rotavirus were reported, which was slightly less compared to 2018 (n=1,140). In 2020, until May, almost half of the rotavirus cases have been observed compared to the same period in 2019 (2019 n=610; 2020 n=284). 43% (62/145) of the typed samples in 2019 corresponded to rotavirus serotype G9. The most prevalent genotypes were G9P8 (26%, 38/145) and G3P8 (28%, 40/145). The Ministry of Health, Welfare and Sport has decided in April 2020 to delay the implementation of rotavirus vaccination in the NIP.

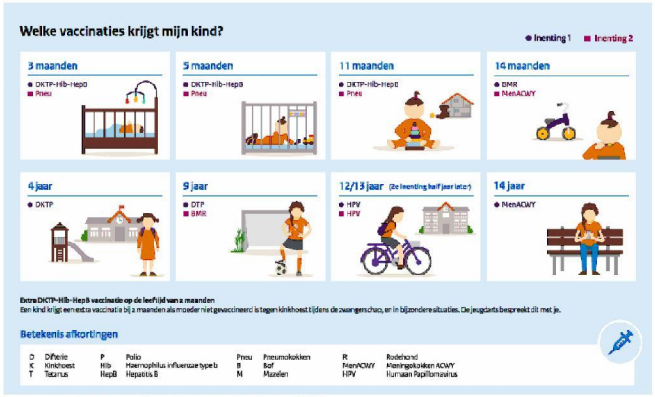
Varicella zoster virus (VZV) infection (varicella and herpes zoster)

The VZV epidemiology (incidence of GP consultations, hospitalisations and deaths) in the Netherlands is comparable to that of previous years; in 2018, GPs recorded about 45,000 varicella and 93,000 herpes zoster episodes (260 and 540 episodes per 100,000 population respectively).
In 2020, the Health Council of the Netherlands issued a positive recommendation to add vaccination against varicella in the NIP in the Caribbean Netherlands and not in the European Netherlands. The council also recommends that residents of these islands who have not yet had an infection be offered a one-off vaccination against VZV.
In July 2020, the revised Dutch guideline 'Varicella' has been published. It includes revised opinions on post-exposure prophylaxis (PEP) and a new module on varicella treatment.

Uitgebreide samenvatting

Het huidige Rijksvaccinatieprogramma (RVP) omvat vaccinatie tegen 12 ziekten, namelijk difterie, kinkhoest, tetanus, polio, *Haemophilus influenzae*-ziekte, mazelen, bof, rodehond, meningokokkenziekte, hepatitis B, pneumokokkenziekte en infectie met humaan papillomavirus (HPV; Figuur 1). In dit rapport worden surveillancedata en wetenschappelijke ontwikkelingen beschreven voor deze ziekten en voor ziekten waarvoor een vaccin (nog) niet in het RVP is opgenomen, zoals rotavirusinfectie, infectie met varicella zoster-virus (VZV; waterpokken en gordelroos), hepatitis A en infectie met respiratoir syncytieel virus (RSV).

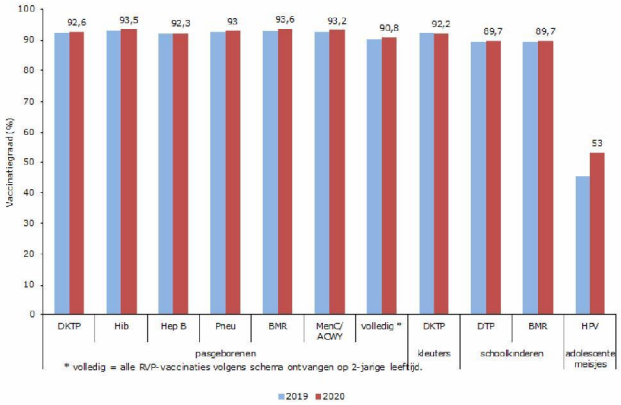
Huidig vaccinatieschema



Figuur 1 Vaccinatieschema van het RVP
Bron: http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/Professionals

Vaccinatiegraad

De landelijke vaccinatiegraad is voor het eerst sinds 5 jaar licht gestegen. Bij zuigelingen, geboren in 2017, geldt dit in het bijzonder voor de vaccinatie tegen bof, mazelen en rodehond (BMR). Deze is met 0,7% gestegen tot 93,6%. De landelijke vaccinatiegraad voor de HPV-vaccinatie (baarmoederhalskanker) voor meisjes, geboren in 2005, is met 7,5% toegenomen tot 53%. De voorlopige landelijke vaccinatiegraad voor de meningokokken ACWY-vaccinatie voor adolescenten geboren in 2001-2005 is hoog (86%).
Het is geruststellend dat het effect van de COVID-19-pandemie op deelname aan de eerste BMR-vaccinatie, ondanks enige vertraging in vaccinatie, beperkt lijkt.



Figuur 2 Vaccinatiegraad per vaccin voor pasgeborenen, kleuters, schoolkinderen en adolescente meisjes in verslagjaar 2019 en 2020
Bron: Præventis

Acceptatie van vaccinatie

Verschillende kwantitatieve en kwalitatieve studies hebben aangetoond dat het belangrijk is om de communicatie en communicatiestrategieën rondom vaccinaties toe te spitsen op de doelgroep(en). Zo blijkt dat de communicatie rondom MenACWY zich zou moeten richten op ouders, maar ook tieners. Verder is het betrekken van relevante zorgprofessionals in het communicatieproces essentieel. Onderzoek naar de maternale kinkhoestvaccinatie (MKV) heeft aangetoond dat vrouwen de informatie het liefst krijgen via hun zorgprofessional (verloskundige, gynaecoloog). Dit geldt ook voor vrouwen die nog niet hadden gehoord of gelezen over MKV. Informatie die op maat gemaakt is zodat het zo goed mogelijk aansluit bij de doelgroep(en) en tijdens spreekuren wordt gegeven kan de acceptatie van vaccinaties verhogen. Deze ontwikkelingen zouden eerst doorgevoerd moeten worden, voordat wordt overgegaan op meer verplichtende maatregelen omtrent vaccineren, omdat onderzoek heeft aangetoond dat verplichtende maatregelen de acceptatie van vaccinaties niet per se verhoogd.

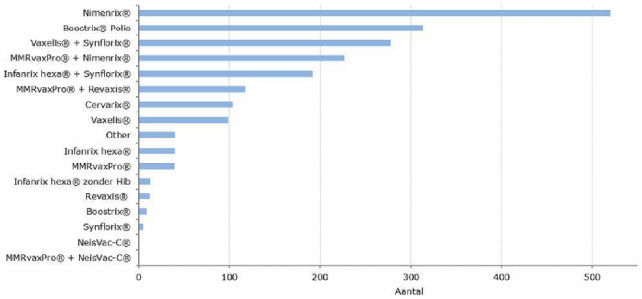
Ziektelast

De geschatte ziektelast veroorzaakt door ziekten die (deels) door vaccinatie te voorkomen zijn, uitgedrukt in Disability Adjusted Life Years (DALYs), was in 2019 het hoogst voor HPV (19.400 DALYs (75% voor vrouwen)), invasieve pneumokokkenziekte (9.500 DALYs per jaar), kinkhoest (2.600 DALYs per jaar), rotavirusinfectie (1.100 DALYs per jaar), invasieve ziekte veroorzaakt door *Haemophilus influenzae* (970 DALYs per jaar) en invasieve meningokokkenziekte (890 DALYs per jaar). Voor de meeste ziekten was de geschatte ziektelast in 2019 vergelijkbaar met de geschatte ziektelast in 2018. De ziektelast van invasieve pneumokokken- en meningokokkenziekte was in 2019 lager,

terwijl de ziektelast van HPV (voor vrouwen), mazelen en kinkhoest in 2019 iets hoger was dan in 2018.

Bijwerkingen

In 2019 ontving Bijwerkingencentrum Lareb 2.009 meldingen van in totaal 7.378 mogelijke bijwerkingen van vaccins. In vergelijking met 2018 is het aantal meldingen gestegen met 32%. Dit wordt hoofdzakelijk veroorzaakt door de inhaalcampagne van de meningokokken ACWY vaccinatie bij 14-18 jarigen. Het aantal geregistreerde mogelijke bijwerkingen na vaccinatie per melding was overeenkomstig met voorgaande jaren (3,7).
Er werden geen nieuwe signalen van verontrustende bijwerkingen gevonden.



Figuur 3 Aantal meldingen van mogelijke bijwerkingen per vaccin(s) in 2019
Bron: Lareb

RVP-brede onderzoeksthema's

Na de implementatie van de COVID-19 maatregelen is de gerapporteerde incidentie van kinkhoest, invasieve pneumokokkenziekte, invasieve meningokokkenziekte en bof gedaald.

Huidig RVP

Difterie
In 2019 werd één mogelijk geval van difterie gemeld met een onbekende vaccinatiegeschiedenis. Hoewel de klinische symptomen zeer verdacht waren voor difterie en de patiënt difterie-antitoxine kreeg als behandeling, werd er geen Corynebacterium gevonden. In 2020 werden tot 1 juni geen gevallen van difterie gemeld.
Een Europese serosurveillance-studie toonde aan dat een substantieel deel van de 40-60-jarigen niet-beschermende DT-spiegels had. Niveaus <0,01 IU/ml varieerden tussen de 4% en 43%. Voor 0,1 IU/ml varieerden deze percentages van 23% tot circa 80%. Het percentage onbeschermden in Nederland was 12,8% (<0,01 IE/ml) en 57,5% (<0,1 IE/ml).

Haemophilus influenzae-ziekte
In 2019 was het aantal meldingen van *Haemophilus influenzae* type b (Hib) ziekte vergelijkbaar met 2018 (39 versus 43 gevallen). Tot mei 2020 zijn 16 Hib-gevallen gerapporteerd, iets meer dan in dezelfde

periode in 2019 (n=10) maar vergelijkbaar met 2018 (n=17). In 2019 was de incidentie van de Hib het hoogst bij kinderen jonger dan 5 jaar (2,0 per 100.000). Na een stijgende trend in incidentie waargenomen tussen 2011 en 2016, stabiliseerde de incidentie zich in de periode 2017-2019. Er waren 19 Hib-gevallen bij kinderen die in aanmerking kwamen voor vaccinatie in 2019, waarvan er negen voldoende waren gevaccineerd, wat resulteerde in een schatting van de effectiviteit van het Hib-vaccin van 93%, vergelijkbaar met voorgaande jaren. In 2019 werd een vergelijkbaar aantal gevallen van niet-typeerbare Hi (NTHi) ziekte gemeld als in 2018 (165 vs. 167), wat duidt op een stabilisatie van de NTHi-ziekte. Er werd geen stijging waargenomen in Hi ziekte door andere serotypen.

Hepatitis B
De incidentie van acute hepatitis B-meldingen (n=104) bleef stabiel in 2019 op 0,6 per 100.000 inwoners. Seksueel contact was de meest gemelde risicofactor voor een acute HBV-infectie, maar de transmissieroute bleef onbekend in een derde van de gevallen. Er werden geen gevallen gemeld van acute hepatitis B onder kinderen geboren na de introductie van universele HBV vaccinatie in 2011. In 2019 bleef genotype A het dominante genotype onder acute HBV-gevallen met 58% van de 74 getypeerde gevallen.
Het aantal nieuw gediagnosticeerde chronische HBV-infecties was 1.205 in 2019, dat overeenkomt met een incidentie van 6,2 per 100.000 inwoners.

Human papillomavirus (HPV)-infectie
De incidentie van baarmoederhalskanker is in 2019 toegenomen tot 9,90 per 100.000 terwijl het aantal doden veroorzaakt door baarmoederhalskanker stabiel is gebleven. De incidentie van andere HPV-gerelateerde kankers was tevens stabiel. In een prospectieve cohortstudie (HAVANA) werd een hoge vaccineffectiviteit (VE) gevonden tegen aanhoudende vaginale infecties tot in ieder geval 9 jaar na de vaccinatie. Deze bevindingen worden bevestigd in meer klinische setting: In een studie naar de vroege effecten van HPV vaccinatie op cervicale laesies in opportunistische screening, hadden volledig gevaccineerde vrouwen (12-24 jaar) een lager risico op hrHPV, ASC-US of erger en (H)SIL of erger. Daarnaast werd in surveillance huisartsendata aangetoond dat het bivalente vaccin ook deels bescherming biedt tegen (ano)genitale wratten. Met betrekking tot seroprevalentie bleek dat type specifieke HPV-seroprevalentie verhogingen werden waargenomen bij niet-gevaccineerde vrouwen tussen 2006-07 en 2016-17 (Pienter-onderzoeken). Bij mannen bleef de algehele HPV-seroprevalentie in dezelfde periode stabiel.

Mazelen
Het aantal mazelen gevallen was relatief hoog in 2019 met 84 meldingen. In de eerste zes maanden van 2020 zijn echter slechts 2 gevallen gemeld. Van juni tot augustus 2019 was er een lokale uitbraak in een gemeente met een lage vaccinatiegraad waarbij 32 gevallen gemeld werden, voornamelijk onder ongevaccineerde kinderen. Genotypen B3 en D8 werden gedetecteerd. De voorlopige analyse van de nationale serosurvey (PIENTER studie) uitgevoerd in 2016/2017 laat

een hoge seroprevalentie zien van 97% beschermende antistoffen tegen mazelen in de algemene Nederlandse bevolking.

Meningokokkenziekte
In 2019 daalde de totale incidentie van meningokokkenziekte na een stijging van 2015 tot 2018. In april tot juni 2020 was het aantal gevallen 80% lager dan in dezelfde periode in de afgelopen vijf jaar, wat mogelijk (deels) gerelateerd met de COVID-19 maatregelen die in deze maanden van kracht waren, waaronder sociale distantiëring en sluiting van scholen. Het aantal gevallen met meningokokken serogroep C is nog steeds erg laag, met zes gerapporteerde gevallen in 2019.
De vaccinatiegraad van de MenACWY-vaccinatiecampagne in 2018/2019 onder 14-18-jarigen was 84% en een extra 2% van de voor vaccinatie in aanmerking komende bevolking werd voorafgaand aan de campagne gevaccineerd. Een lagere vaccinatiegraad werd waargenomen wanneer ouders in het buitenland werden geboren, vooral voor ouders geboren in Marokko of Turkije.
In 2019 daalde de incidentie van meningokokken serogroep W (MenW) ziekte tot 0,39 per 100.000 (n=62), na een toename van het aantal gevallen van 2015 tot 2018. In de eerste zes maanden van 2020 zijn er slechts acht gevallen gemeld zonder meldingen in april tot juni. De afname van MenW in 2019 en de eerste maanden van 2020 werd zowel bij gevaccineerde als bij niet-gevaccineerde leeftijdsgroepen waargenomen. Onder de kinderen die op 14 maanden in aanmerking komen voor MenACWY-vaccinatie, was één gevaccineerd en één niet-gevaccineerd MenW-geval. Onder adolescenten die in aanmerking kwamen voor MenACWY-vaccinatie, waren er geen gevallen van MenW.
De incidentie van meningokokken serogroep B (MenB) ziekte neemt gestaag af sinds eind jaren negentig en is gestabiliseerd op een incidentie van 0,5 per 100.000 sinds 2011. In 2019 werden 72 ziektegevallen en vijf sterfgevallen door MenB gemeld, vergelijkbaar met 2018 (74 gevallen en vijf doden). De incidentie van MenB was het hoogst bij kinderen onder de 5 jaar, met 22 gevallen in 2018 (2,5 per 100.000).
Het aantal gevallen van meningokokkenziekte veroorzaakt door serogroep Y of andere serogroepen is laag en stabiel.

Bof
De incidentie van bof was laag in 2019 (0,8 per 100.000; n=131) maar het dubbele van het voorgaande jaar. De stijging in het aantal meldingen zette door in het eerste kwartaal van 2020, maar stopte abrupt in het tweede kawrtaal van 2020. De meeste bofgevallen in Nederland werden veroorzaakt door het bofvirus genotype G.

Kinkhoest
In 2019 bedroeg de totale incidentie van kinkhoestmeldingen 36,8 per 100.000 vergeleken met 28,4 per 100.000 in 2018. In 2020 tot 1 april bedroeg de incidentie 16,6 per 100.000; deze incidentie werd waarschijnlijk beïnvloed door de controlemaatregelen door de COVID-19 pandemie.
In april en mei 2020 werd de vaccinatiegraad van de maternale kinkhoestvaccinatie geschat op ongeveer 70%. In 2019 waren de schattingen voor de effectiviteit van de maternale kinkhoestvaccinatie in het voorkomen van kinkhoest bij kinderen 0-3 maanden oud 73-90%,

uitgaande van een vaccinatiegraad van 20-40%. Voor 2020 bedroeg de vaccineffectiviteit 93-97%, rekening houdend met een dekking van 50-70%.
De prevalentie van prn-deficiënte stammen in Nederland is in 2018-2020 sterk gestegen.

Pneumokokkenziekte
In april en mei 2020 is het aantal invasieve pneumokokken ziekten (IPD) met 80% gedaald ten opzichte van het vijfjarig gemiddelde, hoogstwaarschijnlijk is dit gerelateerd aan COVID-19 maatregelen. Dit had invloed op de algemene en leeftijdsspecifieke incidentie en tijdstrends van IPD in 2019/2020. In het epidemiologische jaar 2019/2020 (juni tot mei) werden 43 kinderen <5 jaar met IPD gerapporteerd, waarvan slechts één geval werd veroorzaakt door een serotype opgenomen in de 10-valent PCV.
Bij kinderen <5 jaar heeft de introductie van pneumokokkenconjugaat-vaccinatie (PCV) in 2006 geleid tot een grote afname van IPD. Sinds 2013/2014 is de IPD-incidentie bij kinderen <5 jaar echter licht gestegen als gevolg van een langzame toename van IPD veroorzaakt door serotypen die niet worden gedekt door het 10-valente PCV. In andere leeftijdsgroepen werden vergelijkbare trends waargenomen met een zeer lage incidentie van IPD veroorzaakt door vaccinserotypen en een toenemende incidentie van IPD als gevolg van niet-vaccinserotypen, waardoor de algehele impact van PCV-implementatie in gevaar kwam. Vaccineffectiviteit (VE) van ten minste twee doses PCV10 was 89% (95% BI 72-96%) tegen vaccintype IPD. In 2020 zou PPV23-vaccinatie worden aangeboden aan alle 60-, 65-, 70- en 75-jarigen in Nederland. Vanwege de COVID-19-pandemie is echter prioriteit gegeven aan de oudste leeftijdsgroepen, wat betekent dat in het najaar van 2020 alle 73-79-jarigen PPV23-vaccinatie aangeboden zullen krijgen.

Polio
In 2019 en 2020 tot 1 juli zijn er geen gevallen van poliomyelitis gemeld in Nederland, ook niet in Caribisch Nederland.
In een historische aankondiging op Wereld Polio Dag (24 oktober 2019) concludeerde een onafhankelijke commissie van experts dat wild poliovirus type 3 (WPV3) wereldwijd is uitgeroeid. Twee van de drie wildtype poliovirussen (WPV2 en WPV3) zijn uitgeroeid verklaard.
In 2019-2020 bleef poliovirus endemisch in drie landen; Nigeria, Afghanistan en Pakistan. Op 21 augustus 2019 was Nigeria, en dus de Afro-regio, 3 opeenvolgende jaren vrij van wildtype poliovirus. Het certificeringsproces om de 5e van de 6 WHO-regio's wildtype polio-vrij te verklaren is aan de gang en zal waarschijnlijk in 2020 worden afgerond.
Wereldwijd was het aantal circulating vaccine derived poliovirus (cVDPV) in 2019 hoger (368) dan in 2018 (105). Om een wereld vrij van alle poliovirussen in stand te houden, heeft het Global Polio Eradication Initiative (GPEI) in 2019 een Polio Endgame Strategy 2019-2023 uitgebracht.

Rodehond
In 2019 werden geen gevallen van rodehond gemeld. De voorlopige analyse van de nationale serosurvey (PIENTER studie) uitgevoerd in 2016/2017 laat een hoge seroprevalentie zien van 95% beschermende antistoffen tegen rubella in de algemene Nederlandse bevolking. In de

PIENTER studie werd de hoogste vatbaarheid gezien onder kinderen in de orthodox Protestante gemeenschap geboren na de laatste rubella epidemie in 2005. Dit geeft aan dat introductie van rubellavirus in deze gemeenschap kan leiden tot een uitbraak.

Tetanus
In 2019 zijn er geen gevallen van tetanus gemeld. In 2020 werden tot 1 juni twee gevallen gemeld, een oudere vrouw die niet in aanmerking kwam voor routinevaccinatie en een niet-gevaccineerde 12-jarige.
In een Europese seroprevalentiestudie onder 40-59-jarigen waren de seroprotectieniveaus voor tetanus voldoende, waarbij slechts zeer weinig sera geen basisimmuniteit hadden. In de Nederlandse serummonsters, gebaseerd op Pienter3-deelnemers, had slechts 0,3% en 5,2% anti-tetanus-antilichaamspiegels van respectievelijk <0,01 IE/ml en <0,1 IE/ml.

Het vaccinatieprogramma in Caribisch Nederland
Over het algemeen is de vaccinatiegraad in de Nederlandse overzeese gebiedsdelen, inclusief Caribisch Nederland (Bonaire, Sint Eustatius en Saba) hoog. In 2019 zijn op Bonaire en Saba geen ziekten gemeld die door vaccinatie te voorkomen zijn.
Bevindingen uit de Gezondheidsstudie Caribisch Nederland laten zien dat HPV-seroprevalentie hoog was bij personen van ≥15 jaar (34%), waarvan meer dan de helft seropositief was voor ≥2 hoog-risico HPV-typen. De seroprevalentie was aanzienlijk hoger bij vrouwen (51%) dan bij mannen (18%), voornamelijk bij vrouwen van 20-59 jaar. Deze gegevens bevestigen het besluit tot invoering van een gender-neutraal HPV-vaccinatieprogramma en de relevantie voor het overwegen van een bevolkingsonderzoek naar baarmoederhalskanker in Caribisch Nederland.

Potentiële RVP-kandidaten
Hepatitis A
Er werden in 2019 164 hepatitis A gevallen gerapporteerd. Dit is een kleine daling ten opzichte van 2018 (n=188), maar nog steeds hoger dan in de jaren 2011-2016 (80-125 gevallen). Er waren geen nieuwe gevallen gerelateerd aan de MSM-uitbraak van 2016-2018. Wel veroorzaakten twee nieuwe stammen uitbraken onder mannen die seks hebben met mannen (MSM). Ongeveer tweederde van de gemelde gevallen in 2019 betrof een volwassene (≥20 jaar). 41% Van de Nederlandse gevallen was reis-gerelateerd, voornamelijk met reizen naar Marokko.

Respiratoir syncytieel virus (RSV)-infectie
In totaal werden 95 RS-virussen (6,4%) gedetecteerd in 1493 gecombineerde neus- en keeluitstrijkjes van patiënten met een acute luchtweginfectie (ARI), verzameld door peilstationartsen in het respiratoire seizoen 2019/2020, vergeleken met 12% in 2018/2019, 6% in 2017/2018 en 12% in 2016/2017. Vanwege de COVID-19-pandemie werden in de weken 10-20 meer monsters afgenomen met een andere leeftijdsverdeling dan voorgaande seizoenen, wat mogelijk deels het relatief lage percentage RSV verklaart.

Rotavirusinfectie
Er werden in 2019 1,056 rotavirus gevallen gerapporteerd, wat iets minder is dan het aantal gevallen in 2018 (n=1,140). Tot mei 2020 zijn bijna de helft van de rotavirus gevallen geobserveerd, in vergelijking met dezelfde periode in 2019 (2019: n=610; 2020: n=284). 43% van alle getypeerde monsters in 2019 betrof rotavirus serotype G9 (62/145). De meeste geïdentificeerde genotypen waren G9P8 (26%, 38/145) en G3P8 (28%, 40/145). Het ministerie van Volksgezondheid, Welzijn en Sport heeft in april 2020 besloten de implementatie van vaccinatie tegen het rotavirus in het Rijksvaccinatieprogramma uit te stellen.

Varicella zoster virus (VZV)-infectie (waterpokken en gordelroos)
De epidemiologie van VZV (huisartsenbezoeken, ziekenhuisopnames en sterfgevallen) is vergelijkbaar met voorgaande jaren: in 2018 werden door huisartsen ongeveer 45.000 waterpokken- en 93.000 gordelroosepisodes gerapporteerd (respectievelijk 260 en 540 episodes per 100.000 inwoners).
In 2020 heeft de Gezondheidsraad geadviseerd om vaccinatie tegen waterpokken in Caribisch Nederland wel toe te voegen aan het RVP en in Europees Nederland niet. De Gezondheidsraad adviseert ook om bewoners van deze eilanden die nog geen infectie hebben gehad een eenmalige vaccinatie tegen VZV aan te bieden.
In juli 2020 is de herziene Nederlandse richtlijn 'Varicella' gepubliceerd. Deze bevat herziene adviezen over profylaxe na blootstelling (PEP) en een nieuwe module over de behandeling van waterpokken.

1. Introduction

1.1 NIP vaccination schedule

Vaccination of a large part of the population of the Netherlands against diphtheria, tetanus and pertussis (DTP) was introduced in 1952. The National Immunisation Programme (NIP) started in 1957, offering DTP and inactivated polio vaccination (IPV) to all children born from 1945 onwards in a programmatic approach. Nowadays, in addition to DTP-IPV, vaccinations against measles, mumps, rubella (MMR), *Haemophilus influenzae* serotype b (Hib), meningococcal disease, invasive pneumococcal disease, hepatitis B virus (HBV) and human papillomavirus (HPV) are included in the programme (Figure 1.1). In the Netherlands NIP vaccinations are administered to the target population free of charge and on a voluntary basis.

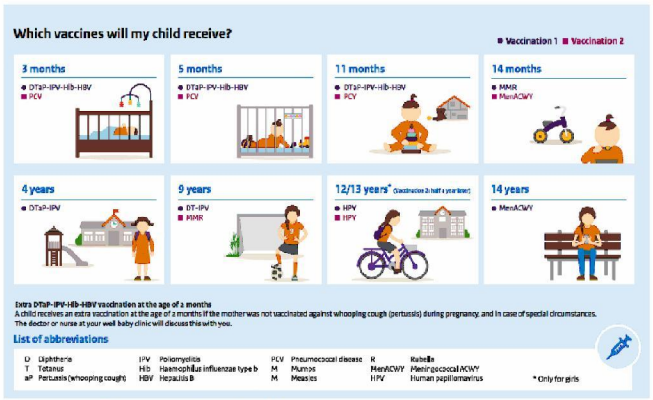


Figure 1.1 NIP vaccination schedule
Source: http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/Professionals

1.1.1 *Changes in the vaccination schedule*

The implementation of maternal pertussis vaccination in the context of the NIP started in December 2019.

1.1.2 *Number of vaccinated children*

In 2019, the vaccination schedule consisted of 12 (boys) or 14 (girls) vaccine doses per child. Of these, 7 were given between 0 and 11 months.
In 2019, 1,520,301 persons (children and pregnant women) were immunised under the Dutch NIP. Together they received a total of 2,929,264 vaccine doses.

1.2 New recommendations and decisions

1.2.1 *New decisions of the Ministry of Health, Welfare and Sport*

In 2020, PPV23 vaccination was to be offered to all 60-, 65-, 70- and 75-year-olds in the Netherlands. However, due to the COVID-19 pandemic,

priority has been given to the oldest age groups, meaning that in Autumn 2020 all 73-79 year olds will be offered PPV23 vaccination.

1.2.2 *New recommendations from the Health Council of the Netherlands*

In 2020, the Health Council of the Netherlands issued a positive recommendation to add vaccination against varicella in the NIP in the Caribbean Netherlands and not in the European Netherlands. The council also recommends that residents of these islands who have not yet had an infection be offered a one-off vaccination against VZV.

1.3 Vaccination of risk groups

Influenza vaccination is offered to people aged 60 years and over, and to those with an increased risk of morbidity and mortality following influenza, through the National Influenza Prevention Programme (NPG). Vaccination against tuberculosis is offered to children of immigrants from high-prevalence countries. For developments with regard to influenza and tuberculosis, please refer to the reports issued by the Centre for Infectious Disease Control (CIb), the Health Council, and the KNCV Tuberculosis Foundation [1-4].
In addition to the vaccination against HBV included in the NIP, an additional vaccination programme that targets groups particularly at risk of HBV due to sexual behaviour and prostitution is in place in the Netherlands [5].
Information on vaccination of travellers and employees at risk of work-related infections can be found on the website www.rivm.nl/vaccinaties.

1.4 Vaccination outside of public vaccination programmes

A number of registered vaccines in the Netherlands are available to the public outside of public programmes. These vaccinations are paid for by the recipient. Relevant information can be found on www.rivm.nl/vaccinaties. Vaccinations registered for infants are those against gastro-enteritis caused by rotavirus infection, varicella, and meningococcal B disease (MenB). For older children and adults influenza, MenACWY and pertussis vaccinations are available. For adults, vaccinations against herpes zoster, pneumococcal disease and pertussis are available. In addition, HPV vaccination for boys, hepatitis A vaccination for MSM, as well as hepatitis B vaccination for first and second-generation migrants from countries where hepatitis B is endemic are available. Professional guidelines for herpes zoster vaccination, pertussis vaccination for adults, HPV vaccination outside the NIP, meningococcal ACWY vaccination, meningococcal B vaccination, rotavirus vaccination, varicella vaccination, pneumococcal vaccination for the elderly, hepatitis B vaccination and hepatitis A vaccination are also available at https://lci.rivm.nl/richtlijnen/. Additionally, guidelines for vaccination of medical risk groups, such as patients with aspleny, are in place.

1.5 Literature

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2. Vaccination coverage

E.A. van Lier

2.1 Key points

- The national immunisation coverage has slightly increased for the first time in five years.
- In infants born in 2017, this applies in particular to the mumps, measles and rubella (MMR) vaccination. This rose by 0.7% to 93.6%.
- The national immunisation coverage for HPV vaccination (cervical cancer) for girls, born in 2005, has increased by 7.5% to 53%.
- The provisional national vaccination coverage for the meningococcal ACWY vaccination for adolescents born in 2001-2005 is high (86%).
- It is reassuring that the effect of the COVID-19 pandemic on participation in the first MMR vaccination seems limited, despite some vaccination delay.

2.2 Tables and figures

Table 2.1 Vaccination coverage (%) per vaccine for age cohorts of newborns, toddlers, schoolchildren and adolescent girls in 2006–2020 [1]

Reporting year	Newborns*							
	Cohort	DTaP-IPV	Hib	HBV[a]	PCV **	MMR	MenC/ ACWY	full ***
2006	2003	94.3	95.4	15.2	-	95.4	94.8	
2007	2004	94.0	95.0	17.1	-	95.9	95.6	
2008	2005	94.5	95.1	17.9	-	96.0	95.9	
2009	2006	95.2	95.9	18.6	94.4	96.2	96.0	
2010	2007	95.0	95.6	19.3	94.4	96.2	96.1	
2011	2008	95.4	96.0	19.4	94.8	95.9	95.9	
2012	2009	95.4	96.0	19.5	94.8	95.9	95.9	
2013	2010	95.5	96.1	19.7	95.1	96.1	96.0	
2014	2011	95.4	95.9	51.4	95.0	96.0	95.8	
2015	2012	94.8	95.4	94.5	94.4	95.5	95.3	
2016	2013	94.2	94.9	93.8	93.8	94.8	94.6	
2017	2014	93.5	94.2	93.1	93.6	93.8	93.5	91.2
2018	2015	92.6	93.4	92.2	92.8	92.9	92.6	90.2
2019	2016	92.4	93.1	92.0	92.6	92.9	92.6	90.2
2020	**2017**	**92.6**	**93.5**	**92.3**	**93.0**	**93.6**	**93.2**	**90.8**

Table continued on next page

Reporting year	Toddlers*				Schoolchildren*			Adolescent girls*	
	Cohort	DTaP -IPV[b]	DTaP -IPV[c]	DTaP -IPV[d]	Cohort	DT -IPV	MMR ****	Cohort	HPV
2006	2000	92.5	1.4	93.9	1995	93.0	92.9		
2007	2001	92.1	1.6	93.7	1996	92.5	92.5		
2008	2002	91.5	1.6	93.1	1997	92.6	92.5		
2009	2003	91.9	2.0	93.9	1998	93.5	93.0		
2010	2004	91.7	2.6	94.3	1999	93.4	93.1		
2011	2005	92.0	2.6	94.7	2000	92.2	92.1		
2012	2006	92.3	2.1	94.4	2001	93.0	92.6	1997	56.0
2013	2007	92.3	2.4	94.7	2002	93.1	92.9	1998	58.1
2014	2008	92.0	2.4	94.4	2003	92.7	92.4	1999	58.9
2015	2009	91.9	2.2	94.1	2004	92.7	92.7	2000	61.0
2016	2010	91.5	2.1	93.7	2005	92.0	92.0	2001	61.0
2017	2011	91.1	2.1	93.2	2006	90.8	90.9	2002	53.4
2018	2012	90.4	2.3	92.7	2007	90.0	90.1	2003	45.5
2019	2013	90.3	2.2	92.5	2008	89.5	89.5	2004	45.5
2020	**2014**	**89.9**	**2.4**	**92.2**	**2009**	**89.7**	**89.7**	**2005**	**53.0**

* Vaccination coverage is assessed at the ages of two years (newborns), five years (toddlers), 10 years (schoolchildren), and 14 years (adolescent girls).

** Only for newborns born on or after 1 April 2006.

*** Key figure full participation newborns: received all NIP vaccinations at two years of age.

**** Two MMR vaccinations (in the past 'at least one MMR vaccination' was reported).

[a] Percentage of the total cohort. Universal hepatitis B vaccination was introduced in 2011; only risk groups were vaccinated previously.

[b] Revaccinated toddlers.

[c] Toddlers that reached basic immunity at age 2–5 years and were therefore not eligible for revaccination at toddler age.

[d] Sufficiently protected toddlers (sum of [b] and [c]).

Source: Præventis

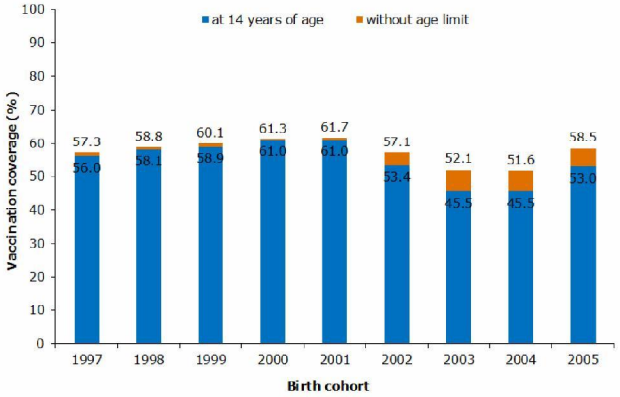

Figure 2.1 HPV vaccination coverage determined at 14 years of age and without age limit, by birth cohort [1]

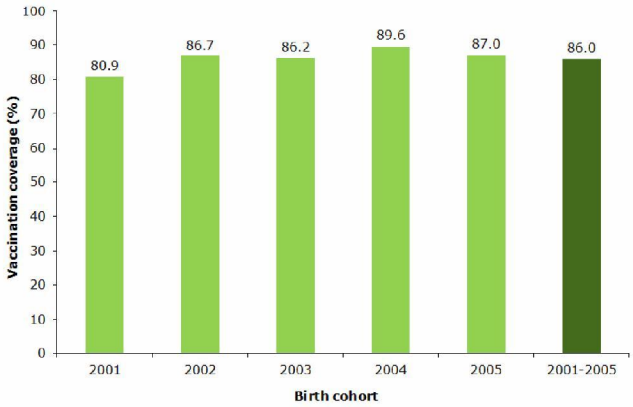

Figure 2.2 Vaccination coverage for meningococcal ACWY vaccination for adolescents, by birth cohort (preliminary figures) [1]

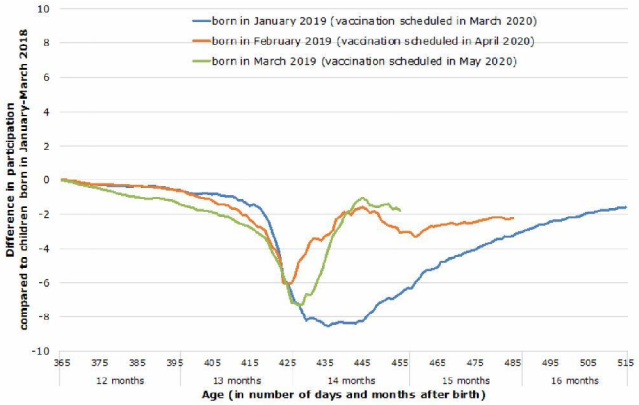

Figure 2.3 Difference in participation in the first measles-mumps-rubella vaccination (MMR1) of children born in January-March 2019 compared to children born in January-March 2018
Note: Children are scheduled to be vaccinated at the age of 14 months. Children born in January, February and March 2019 were scheduled to be vaccinated in March, April and May 2020, respectively. A difference of -8 at 436 days after birth means that the percentage vaccinated for children born in January 2019 (scheduled to be vaccinated in March 2020) at that age was 48% instead of 56% for children born in January 2018.

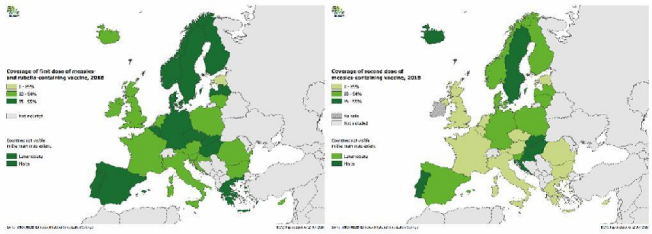

Figure 2.4 Vaccination coverage for first (left) dose of measles and rubella-containing vaccine and second (right) dose of measles-containing vaccine, EU/EEA and the UK, 2018 [2]

2.3 Vaccination coverage

2.3.1 *National developments*

The national vaccination coverage for most vaccinations has increased slightly compared to last year (Table 2.1). In infants born in 2017, the increase for the MMR vaccination is greatest (+0.7% to 93.6%). The increase (+7.5%) in the national HPV vaccination coverage to 53% for girls born in 2005 is striking. The provisional vaccination coverage among girls who are one year younger is currently already at 59% and

is expected to increase even further. In addition, the results for HPV also showed a catch-up effect (vaccination after the age of 14 years), especially for the birth cohorts 2002 to 2005 (Figure 2.1). Furthermore, the national participation among adolescents born in the period 2001-2005 in the MenACWY vaccination is high (preliminary vaccination coverage 86% (Figure 2.2); some of these adolescents will receive another reminder).
In toddlers born in 2014 we see a slight decrease (-0.3% to 92.2%) in the national vaccination coverage for DTaP-IPV (Table 2.1). However, it concerns children who were less often vaccinated against DTaP-IPV as an infant (-0.7%: 93.5% for children born in 2014 versus 94.2% for children born in 2013). Some of the children therefore caught up with the vaccination at a later time, as the difference at the age of five years has narrowed [1].

So for the first time in five years, there has been a slight increase in the vaccination coverage. The extra media attention for the subject of vaccination and the various national and regional initiatives aimed at increasing the vaccination coverage seem to be bearing fruit. The threat of the meningococcal W outbreak may also have played a role. Hopefully, this improvement in vaccination coverage will continue in the future because the vaccination coverage has not yet returned to its old level of about six years ago [1].

2.3.2 *Future challenges*

2.3.2.1 Effect of COVID-19 pandemic

The vaccination coverage in Table 2.1 concerns children who have been vaccinated before 2020. It is currently unclear to what extent the COVID-19 pandemic will have an effect on vaccination coverage in the coming years. The extent of the effect of this pandemic on the vaccination coverage depends on the duration of the crisis and whether missed vaccinations are still made up (in time). Preliminary data (situation at 16 july 2020) showed that the participation of children in the first MMR vaccination (given around 14 months of age) who are scheduled to be vaccinated in March-May 2020 was delayed. However, as a result of catch-up vaccination, participation now is only ~2% lower compared to the previous year (Figure 2.3). More children are expected to be vaccinated in the coming months. The final vaccination coverage is not determined until the age of 2. For children born in 2019 and 2020, this will be done in the years 2022 and 2023. At the moment it is still too early to be able to say anything about participation in older age groups.

2.3.2.2 Differentiation NIP and informed consent

Insight into vaccination data at individual level, through the national registration system Præventis, has so far made it possible to identify small changes in vaccination coverage in a timely manner. For example, the signal of the declining vaccination coverage, which has now turned, could be taken up professionally by many, but especially by the NIP implementers. However, from 2020 the complexity of the vaccination schedule, and with it the vaccination coverage calculation, will increase. In order to continue to detect changes in the vaccination coverage in time, additional information is needed, such as whether a child was premature at birth and whether his/her mother was vaccinated against whooping cough during pregnancy. At the moment not all necessary additional information is available. It is also not known which part of the population will consent to the exchange of vaccination data between JGZ and RIVM in the future by means of the informed consent that will be implemented [1].

2.3.3 *International developments*

Over 100,000 measles cases were reported in the WHO European Region for the period January to October 2019. This number exceeds the 2018 total and is over three times the total reported in 2017. These figures highlight that although measles vaccination coverage has improved overall in the region, many people remain susceptible [3].
Only five countries (Hungary, Malta, Portugal, Slovakia, and Sweden) in the European Union/European Economic Area (EU/EEA) reported at least 95% vaccination coverage for both the first and second doses of measles- and rubella-containing vaccine in 2018 (see Figure 2.4) [2].
In 2018, vaccination coverage for the first dose rose to above 95% in Finland and Malta and dropped to below 95% in Austria compared to 2017. For the second dose, vaccination coverage rose to above 95% in Malta compared to 2017 [2].

2.3.3.1 Effect of COVID-19 pandemic

In other countries such as England and the United States, the first MMR and DTaP-IPV vaccinations also showed a decrease when the COVID-19 pandemic started. However, this decrease was larger than in the Netherlands. Abroad, too, after an initial sharp decline, the proportion of children vaccinated increased again after some time [4-6].

2.4 Literature

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2.1.2 *Other recent RIVM publications*

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3. Acceptance of vaccination

K. van Zoonen, T. M. Schurink-van t Klooster, C. Oostdijk, M. de Vries, M. D. Wennekes, H. de Melker, E. Rikkengaa, L. Visser, L. Mollema

3.1 Key points

- A questionnaire study showed that health care workers are the most important source of information for women regarding the MPV.
- Quantitative and qualitative studies showed communication regarding the MenACWY vaccination should emphasize the safety and effectiveness of vaccines, and should focus on both teenagers and parents.
- Tailored information and/or consultation especially for target groups that are associated with lower HPV-vaccination might help to increase the HPV-vaccination uptake.
- International studies showed mandates alone are not necessarily effective in increasing vaccine acceptance and therefore uptake.

3.2 Monitoring acceptance NIP

Acceptance of the NIP and specific vaccines as well as intention to get vaccinated is monitored by the RIVM. In this chapter several studies are discussed regarding some relevant developments in the NIP. For example, the maternal pertussis vaccination was included in the Dutch NIP. With the inclusion of the maternal pertussis vaccination, the current NIP now includes vaccinations from pre-birth up to 14 years of age. However, prior to its inclusion the vaccine was available to pregnant women as an 'additional' vaccine (i.e. available at own request and costs). Furthermore, the Ministry of Health, Welfare and Sport decided to adopt the Health Council's advice on the HPV vaccination [1]. Other developments were the MenACWY vaccination "catch-up campaign" for adolescents and the inclusion of the MenACWY vaccination to the NIP for infants and adolescents. There was also an advice about the pneumococcal vaccination for the elderly [2]. Furthermore, several studies have focused on strategies and interventions that might increase vaccine uptake (such as mandates).

3.3 Pregnancy (pre-birth)

3.3.1 *Maternal pertussis vaccination*

Before the maternal pertussis vaccination (MPV) was included in the NIP (end of 2019), the RIVM conducted a study among pregnant and nonpregnant women focusing on their awareness, information seeking behaviour and vaccination uptake. The study aimed to examine whether (extra) communication efforts regarding MPV lead to awareness among women. The women that were not pregnant at the time of the study, had to have a child under the age of two years. This would mean the women had been pregnant after the decision of the minister in 2017 to include the vaccine in the NIP, but before it was decided when the vaccination would be included in the NIP. During this period, the communication about the vaccination was increased (e.g. information flyers and factsheets for health care professionals (HCPs) as well as the public were made available). A total of 942 women were included of

which 358 women were pregnant (38%). The study showed that most women are aware of MPV and engaged with MPV (i.e. felt MPV was an important topic to them). Women in both groups reported their HCW as preferred source of information. In addition, the public health institute (PHI) website was mentioned as a source for (additional)information. This study was conducted before the implementation of MPV and showed a relatively high percentage of women who reported to have been vaccinated during their (last) pregnancy (43% of all pregnant and 38% of nonpregnant women). This indicates that the (extra) communication strategies about the vaccination might have been effective in increasing awareness and possibly uptake. This is most likely due to educating the relevant HCP on maternal pertussis vaccination as well as including them in providing the information to the target group (e.g. pregnant women). However, these percentages might also be relatively high because women were relatively motivated by the topic and we used self-reported measures.

3.4 Adolescents

3.4.1 *MenACWY*

To prepare for and to assess the implementation (of the MenACWY vaccination) and the catch-up campaign in late-2018 and its expansion in 2019, several studies at the RIVM were conducted; one focused on knowledge, beliefs and intention to vaccinate in adolescents and parents before the vaccination, and another focused on the decision-making process and actual vaccination behaviour [3].
With the aim to study what teenagers and their parents knew and believed about meningococcal disease, the MenACWY vaccination, and vaccinations in general, and which aspects of knowledge and specific beliefs predict MenACWY vaccination intentions of teenagers and their parents. Adolescents who were invited for the menACWY catch-up vaccination campaign and their parents were surveyed about their knowledge and beliefs about meningococcal disease, the menACWY vaccination, vaccinations in general, and menACWY vaccination intentions. Random forest analysis was applied to study predictions of vaccination intentions by these knowledge and beliefs. The survey response rate was 52.8% among teenagers (N=1,603) and 57.1% among parents (N=1,784). Adolescents and their parents were generally inclined to receive the menACWY vaccination. Both groups seemed aware of the severity and contagiousness of invasive meningococcal disease (IMD), but there were also knowledge gaps and misbeliefs. For example, we found a relatively strong agreement in our study population for the misbelief that vaccines annually cause the death of several children in the Netherlands. Knowledge and beliefs concerning the effectiveness of, need for, and safety of vaccines in general were the strongest predictors of menACWY vaccination intentions in parents, surpassing knowledge and beliefs about meningococcal disease and the menACWY vaccination. For adolescents, the will of their parent(s) was the strongest predictor of their own vaccination intention. For future communication accompanying vaccination campaigns combatting outbreaks, the authors recommend concentrating on filling knowledge gaps and addressing specific misbeliefs about the effectiveness and safety of vaccines. In addition, to optimize vaccination uptake during future outbreaks, the authors recommend emphasizing the effectiveness

and safety of vaccines to parents and continuing to focus communication efforts on both parents and adolescents [3].
The study regarding the decision-making process about the menACWY vaccine consisted of a qualitative and a quantitative part. The aim was to gain insight into how households/parents and adolescents make a decision regarding the menACWY vaccination. It looked at what factors influenced both parents and adolescents during their decision-making and what they needed to make such a decision. It targeted parent and adolescent dyads who were invited to the catch-up campaign of late 2018 and early 2019. The qualitative part consisted of 20 households, totalling 38 interviews (20 parents/18 adolescents). Of these, seven households (7 parents/5 adolescents) had decided not to get the menACWY vaccine. The quantitative part consisted of 1,093 parents and 878 adolescents who completed an online questionnaire. This resulted in 506 parent/adolescent dyads, with others being the sole participant from their household. Among the parents 87% reported their child getting the menACWY vaccine. Among the adolescents 92% reported getting the menACWY vaccine.
The deliberations people made when deciding about the menACWY vaccination were partly related to ideas specifically concerning meningococcal disease and the vaccination itself and partly influenced by previously held convictions about vaccinations.
During interviews parents of vaccinated adolescents mentioned that the disease "seems scary", that infection "can happen just by getting sneezed on" and that the possible rapid progression of the disease contributed to making a swift decision. Simultaneously they indicated that "vaccinating is just a given" and is something they "do not really think about". The questionnaire showed that among the households where the adolescent had been fully vaccinated according the National Immunisation Programme (NIP), the majority (93%) also chose to get the menACWY vaccine.
Of the parents who got their child vaccinated 83% indicated not thinking about their decision very long. The opposite was the case among parents whose adolescent did not get the menACWY vaccine. A majority of these parents (61%) indicated that they had elaborately deliberated about their decision and thus had not made a swift decision.
Most parents discussed the choice for or against the menACWY vaccine with their child. But the preference of the parent(s) was often determinative for the final decision within a household. However, the adolescents experienced this differently. Of the adolescents, 23% indicated they themselves had made the final call on whether or not to get the menACWY vaccine. This contrasts with only 5% of parents who indicated their child made the final call for themselves
Parents and adolescents from the same households – either vaccinated or not - had corresponding attitudes, made similar deliberations and had similar reasons for their decisions. The most mentioned reasons not to get vaccinated were the low risk of getting meningococcal disease and the idea that the vaccine is not good for your health. Adolescents also specifically mentioned a dislike or even fear of getting vaccinated.
Insight into the decision-making processes of both parents and adolescents provides an understanding of the intra-household dynamics that occur with vaccinations targeting adolescents. This in turn offers insight into different decision-making processes for those accepting and those rejecting this vaccination and provides opportunities to target

communications more effectively aimed at those most influential in the different ways of decision-making.

3.4.2 *HPV*

The vaccination coverage of HPV for adolescent girls is still relatively low in the Netherlands. A literature study was conducted to examine the strategies that were put in place in order to increase vaccine uptake in Europe [4]. The age at which the vaccine is administered varies widely across Europe, between 9 and 15 years old. Furthermore, the setting in which the vaccine is administered varies. Ireland and Denmark have developed tailored information/education for HCP as well as the public. They used social media extensively and set up an alliance with several stakeholders. Literature shows that using reminders (before the vaccine is administered), a no-show policy, tailored information/education, reporting the vaccine coverage to HCP and lowering barriers to receiving the vaccine will lead to an increase in vaccine-uptake between 10 to 20%. It remains highly important that HCP promote the vaccine and help counter misinformation and/or misperception about the HPV-vaccine [4].
The Dutch Health Council advised to also vaccinate boys and lower the vaccination age to the year in which children turn 10 years old and the exploration of the possibilities of offering the HPV vaccine up to the age of 26. To gain insight in the number of vaccines needed, the RIVM conducted a study which aimed to explore the intention to vaccinate among (parents of) boys and the younger and older target groups. For this study unvaccinated girls and boys 9 to 17 years of age were randomly selected from the national vaccination registry (Praeventis). In addition, young women and men 18 to 26 years of age were randomly selected from the population registry. Selected persons (or the parents in case the adolescent was younger than 16 years of age) received an invitation letter with a link to a webpage with some basic information on HPV-vaccination and a link to an online questionnaire containing questions about the intention and attitude to HPV-vaccination. Participants that were already vaccinated (301 of the 1091), didn't have to answer the questions on intention and attitude.
The participation was 9.6% (n=191) and 9.2% (n=367) for the (parents of) younger (9-17 yr) and older (18-26 yr) girls respectively. For (parents of) younger and older boys the participation was 6.5% (n=392) and 7.1% (n=141), respectively. Results showed that the intention and attitude among girls varied between 15-69%, which was the highest among the youngest girls 9-10 years of age and very low among girls 18-21 and 22-26 years of age. The intention and attitude was higher among boys than among girls, i.e. varying between 56-79%, and the highest among the youngest boys 9-10 years of age and oldest boys 22-26 years of age. The most important reasons to vaccinate were protection against cancer, expected regret in case of no vaccination and getting cancer, and because it's offered by the government. The most important reasons not to vaccinate were adverse events and the uncertainty of long-term effects.

3.4.3 *HPV for boys*

In order to provide input on the parents' views and awareness of the HPV vaccination for boys, the RIVM recently conducted a qualitative study that focused on their beliefs, associations about HPV vaccination

for their nine/ten year old son and their intention to vaccinate their son against HPV. Parents were interviewed over the phone and asked about their associations with HPV and the HPV vaccine as well as with vaccinations in general. Furthermore, questions regarding their attitude towards and intention to vaccinate their son against HPV. They were also asked about their views on several visual presentations about HPV vaccination. This information will be used in the upcoming public campaign when HPV vaccination for boys will be implemented.
In another sub-study, visuals on HPV vaccination are developed to make parents aware of the link between HPV infection/ vaccination and cancer, and to enhance their understanding of the risk of HPV infection and effectiveness of the vaccination. The visuals will be tested on relevance and usability in focus group interviews with parents. The effectiveness and underlying mechanisms of the visuals will be assessed in a quantitative study. Results of these studies are expected in the fall of 2020.

3.5 Adults

3.5.1 *Pneumococcal vaccination for the elderly*

In the fall of 2020 elderly people (e.g. 73 up to 79 years old) will be invited to get vaccinated against pneumococcal disease [2]. The state secretary follows the advice given by the Dutch Health Council in April 2020 stating that people who are 73 years or older are at higher risk for a more severe course of pneumococcal disease compared to those aged 60 to 72 years.
An international project where the National Institute for Public Health and the Environment participates in, VITAL, is currently being conducted. One focus is to work out ways to educate and train HCPs involved in caring for older adults regarding the importance of vaccinations for this age group.
An important step is to understand perceptions of older adults regarding elderly vaccination. This has been studied by conducting focus groups among older adults in Hungary, France, Italy and The Netherlands. Preliminary results indicated a strong need among older adults for more information on vaccines. They would like to receive information on: side-effects, effectiveness of the vaccine, susceptibility for the disease and safety of the vaccine when combined with pre-existing health problems. The GP, and to a lesser extent specialists and pharmacists, play an important role in the information provision on vaccines to older adults.
Another step is to understand the perspectives of HCPs on vaccines for older adults. As well as what information needs HCPs may have regarding these vaccines. In 2020/2021 individual interviews with HCPs will be conducted. The results of these interviews will be validated quantitatively by means of a questionnaire. Furthermore, two literature reviews are being conducted which focus on identifying educational interventions for HCPs that have proven to be effective, as well as barriers HCPs experience in the communication with older adults on vaccines.

3.6 Communication

From December 2019 onward the maternal pertussis vaccination is included in the NIP. It is called the "22-weeks shot" and can be administered to pregnant women who are at least 22 weeks pregnant. Specific communication materials were developed, such as an

information pamphlet (available in several languages), posters and a website (www.22wekenprik.nl). The materials were pretested in the target group.
Through the website women can make an appointment at the youth health care centre in their neighbourhood. Prior to the introduction of MPV a public campaign was started. This campaign consisted of advertorials/articles in magazines (online and print), banners, a video and materials to include in free giftboxes for pregnant women. During this first period of administrating MPV the women all received a pink band-aid.
The HPV vaccine for boys will also be included in the NIP in the near future. This means that all 9 year old children, boys and girls, will receive an invitation to get the HPV vaccination. It will be possible to receive this vaccination for free to all Dutch citizens until they are 26 years old.
A public campaign will be part of this introduction to make the Dutch citizens aware. The most important target groups will be parents of 9/10 years old children, adolescents up to the age of 16 years, young adults up to the age of 18 years and HCPs. The goal is to make a clear and tailored message to all target groups to maximize acceptance of, and intention to get vaccinated with, the HPV vaccination. We will use behavioural knowledge to put emphasis on the prevention of cancer (not just HPV) and use narrative stories of (ex)patients and their family members/friends. There will also be a focus on the (media)dynamics regarding HPV and many external parties have indicated to be willing to partner up.

3.7 Strategies and interventions to increase vaccine uptake

Several strategies to increase vaccine uptake in a sustainable way are discussed during several conferences and reported on in articles [5, 6]. For example, it was identified that parents should seek information about vaccines from scientific and medical sources that are not based on misinformation and unproven alternatives. Also, health care professionals (HCP) need tools and training in order for them to effectively engage in vaccination acceptance conversations with parents. The role of mandates is also discussed, but as other research in countries with mandates has shown this should be complemented with other strategies, such as more time for HCP to the practice of vaccination counselling [5, 7].
In the Netherlands, Nivel and Amsterdam UMC conducted a study examining the effectiveness of measures to increase vaccine uptake and examined the suitability of these measures to the Dutch context [8]. They identified four types of measures; 1) mandates; 2) financial incentives; 3) measures that support the logistics of vaccination; 4) communication and promoting knowledge. They conclude that the first two types are less suitable to the Dutch context. However, it is likely that only a small portion of people that refuse vaccinations will be motivated to receive vaccinations by removing practical barriers (such as forgetting an appointment). When people refuse vaccinations based on religion it would be more suitable to focus on communication and knowledge enhancement. Furthermore, they conclude that it is necessary to get a better view of people who do not vaccinate and for what reasons in order to make sure the most adequate measure is chosen to increase the vaccine uptake. Also, the measures discussed in

the study, which were introduced in other countries, lack evaluation which makes it difficult to interpret the effectiveness.

3.8 International literature and studies

3.8.1 *MenACWY*

In the UK several studies were conducted to examine the influence of school characteristics and/or area-level factors on the uptake of MenACWY vaccine [9, 10].
One study focused on five school characteristics; overall effectiveness score (i.e. Ofsted; Effectiveness scores at schools last inspection); type of school; number of pupils eligible for the MenACWY vaccine within the school; percentage of total school population eligible for free school meals; percentage of total school population with English as a second language [10]. This study showed that the overall uptake rate was 80.7% and uptake rates were associated with all five school characteristics considered. Effectiveness scores for schools (i.e. quality of education, behaviour and attitudes, personal development of pupils, leadership and test results) had the largest association with vaccine uptake, with poorer schools having lower uptake. Another study showed that independent, special schools and pupil referral units had lower vaccination coverage compared to state-funded secondary schools [9].
In the US menACWY vaccination is a recommended routine vaccination administered at ages 11-12 years with a booster at age 16 years [11, 13]. However, the uptake is lower in older adolescents. One study also showed that especially non-college adolescents bear the disease burden as the vaccine rates are lower (38-57%) compared to college-bound adolescents (90%-100%) [11]. A study identifying factors associated with MenACWY uptake among adolescents showed that younger adolescents more often received MenACWY vaccination compared to older adolescents [12]. This was largely explained by the difference in healthcare utilization (i.e. older adolescents have fewer preventive care visits and interaction with non-paediatric healthcare providers). This indicates that unique strategies might be necessary to increase uptake among older adolescents, such as encouraging annual preventive care visits in adolescents aged 16 to 18 years [12]. Another study showed significant influence of state of residence on the likelihood of MenACWY vaccine completion and compliance [13]. This was mainly due to state-level determinants, such as paediatrician-to-children ratio and the proportion of Immunization Information System use among adolescents.

3.8.2 *HPV*

A literature review focused on summarizing all peer-reviewed and grey literature published about determinants of HPV vaccine hesitancy Europe. They state that Europe is increasingly described as a region with the least confidence in vaccination and the safety of vaccines. Determinants differed by country and population groups. Tailored and context-specific interventions are, therefore, essential to improve confidence in HPV vaccination and build public trust [14]. Other studies support this view. For example, a study conducted in the UK focused on the influence of school-level and area-level factors on HPV vaccine coverage [9]. Muslim and Jewish schools had lower coverage compared to schools with no religious character. Also, independent, special schools had lower vaccination coverage compared to state-funded secondary schools. Tailored approaches are necessary to increase HPV vaccine

uptake in Muslim and Jewish schools [9]. A cross-sectional study conducted in Italy focusing on individual factors that influence HPV vaccine hesitancy suggests that communication and education strategies must be undertaken to ensure parents are fully informed and (relevant) HCP should be included to provide information about the risks of contracting HPV infection and vaccine usefulness [15].
A study, indicating that HPV vaccination in the UK will soon be extended to boys and that vaccine uptake for boys might initially be lower in boys compared to girls, examined what would influence parents' (who's child is eligible for HPV vaccination within 3 years) willingness to vaccinate, not vaccinate or remain undecided about vaccinating their child [16]. The results indicated that previous vaccine refusal (in general) was the strongest predictor of not wanting the HPV vaccine. However, awareness of HPV and HPV vaccine as well as a positive attitude were associated with the decision to vaccinate. This suggests that there is a need for the public to become more aware through public health campaigns [16].
Another study focusing specifically on HPV vaccination for boys in Sweden showed that participants were in favour of introducing HPV vaccinations for boys in the NIP [17]. Furthermore, in Slovenia the inclusion of HPV vaccination for boys is planned for schoolyear 2020/2021. The HPV for boys is currently paid by municipalities and the study examined the results on vaccine uptake. The study showed that acceptance of HPV vaccination for boys in Slovenia is adequate (ranging from 25% to 69%) and this will lead to significant results when it is included in the NIP of Slovenia. The current success of the vaccination coverage (i.e. coverage rates are comparable or even higher than those in the NIP for girls) is contributed to excellent local initiatives of several HCP and school medicine specialists [18].

3.9 Literature

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*RIVM publication

4. Burden of disease

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4.1 Key points

- The estimated burden of disease caused by (partially) vaccine-preventable diseases expressed in Disability Adjusted Life Years (DALYs) for the year 2019 was highest for HPV (19,400 DALYs (75% among women)), invasive pneumococcal disease (9,500 DALYs/year), pertussis (2,600 DALYs/year), rotavirus infection (1,100 DALYs/year), invasive *Haemophilus influenzae* disease (970 DALYs/year), and invasive meningococcal disease (890 DALYs/year).
- For most diseases, the estimated burden in 2019 was comparable to the estimated burden in 2018. The disease burden of invasive pneumococcal and meningococcal disease was lower in 2019, whereas the burden of HPV (for females), measles and pertussis was somewhat higher in 2019 than in 2018.

4.2 Tables and figures

Table 3.1 Estimated annual disease burden in DALYs in 2015–2019, and DALYs per 100 infections in 2019 in the Netherlands (with 95% uncertainty intervals) [1, 2]

Disease	DALYs (95% uncertainty interval)					DALYs/100 infections
	2015	2016	2017	2018	2019	
Diphtheria	4 (3–5)	2 (2–3)	4 (3–4)	3 (3–4)	0 (0–0)	n/a
Hepatitis A virus infection	43 (27–72)	44 (27–73)	200 (120–340)	100 (62–170)	90 (55–150)	11 (8–15)
Hepatitis B virus infection (acute)	100 (95–110)	180 (170–190)	150 (140–160)	130 (120–140)	120 (110–120)	23 (21–23)
Human papillomavirus infection[a]						
- Females	12,000 (11,200–12,800)	13,200 (12,400–14,000)	12,900 (12,100–13,800)	13,800 (13,000–14,700)	14,600 (13,800–15,400)	n/a
- Males	4,900 (4,100–5,900)	5,300 (4,400–6,400)	5,200 (4,200–6,300)	5,400 (4,400–6,400)	4,800 (4,000–5,800)	n/a
Invasive *H. influenzae* disease	840 (800–890)	860 (800–910)	980 (930–1,000)	1,000 (960–1,100)	970[b] (920–1,000)	380 (360–400)
Invasive meningococcal disease	560 (440–700)	880 (730–1,000)	1,100 (970–1,300)	1,100 (970–1,300)	890[c] (740–1,100)	530 (490–580)
Invasive pneumo-coccal disease	10,900 (10,200–11,500)	9,800 (9,200–10,500)	9,800 (9,200–10,400)	10,800 (10,100–11,400)	9,500[d] (8,900–10,100)	360 (340–380)
Measles	1 (1–1)	1 (1–1)	3 (2–3)	5 (4–5)	16 (15–18)	2 (2–2)
Mumps	0.7 (0.6–0.7)	0.5 (0.5–0.6)	0.4 (0.3–0.4)	0.6 (0.5–0.6)	1 (1–1)	0.4 (0.4–0.4)
Pertussis	2,700 (2,500–2,900)	1,500 (1,400–1,600)	2,000 (1,900–2,200)	2,000 (1,900–2,100)	2,600 (2,500–2,800)	1 (1–1)
Poliomyelitis	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	n/a
Rabies	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	n/a
Rotavirus infection	1,300 (520–2,500)	670 (280–1,300)	1,100 (440–2,200)	1,200 (470–2,400)	1,100 (440–2,300)	0.5 (0.3–1)
Rubella	0.06 (0.04–0.08)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	n/a
Tetanus	9 (7–10)	2 (2–2)	0.6 (0.5–0.8)	1 (1–1)	0 (0–0)	n/a

DALY= disability-adjusted life years

n/a = not applicable; no cases occurring in 2019 or unknown number of infections (HPV)

[a] To estimate the burden, the numbers of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV were used. The most recent year of available data on the incidence of anogenital warts and high-grade cervical lesions was 2016 and 2018, respectively. Therefore, the incidence rate of anogenital warts for 2016 was carried forward to 2017–2019 and the incidence rate of high-grade cervical lesions for 2018 was carried forward to 2019.

[b] Proportion caused by the vaccine-preventable type b in 2019: 28%.

[c] Proportion caused by the vaccine-preventable type C in 2019: 3%; proportion caused by type B in 2019: 59%; proportion caused by type W in 2019: 29%.

[d] Proportion caused by the vaccine-preventable types 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F in 2019: 4%.

Sources: OSIRIS, NRLBM, sentinel laboratory surveillance, national cancer registry, PALGA, NIVEL-LINH

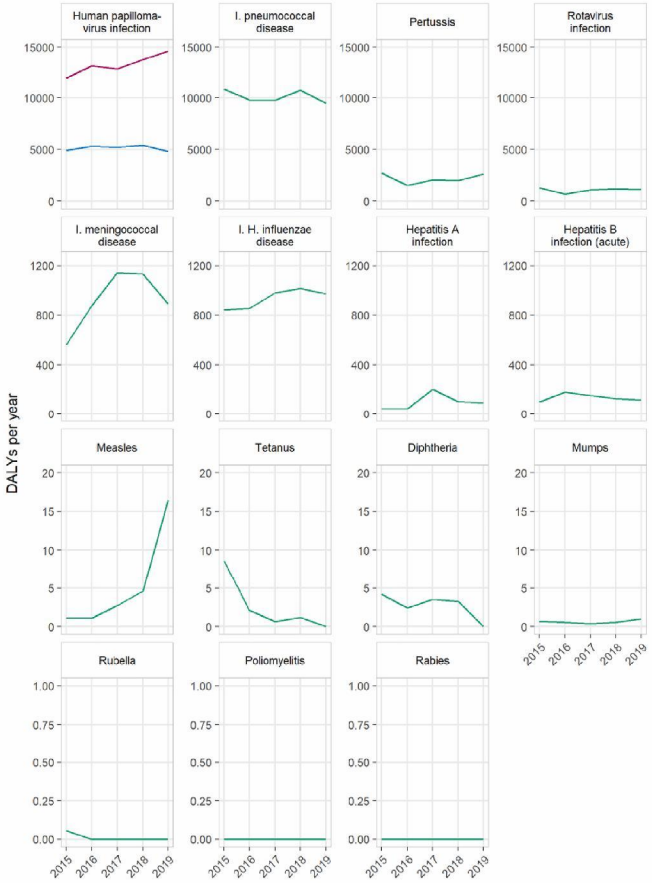

Figure 3.1 Estimated annual disease burden in DALYs in 2015–2019 in the Netherlands [1, 2]
1. Vaccination against rabies, hepatitis A and rotavirus infection is not included in the NIP.
2. For the three invasive diseases, a vaccine was only available against certain serotypes: Haemophilus influenzae serotype b (Hib), meningococcal ACWY and pneumococcal serotype 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F. For HPV infection, a vaccine was only available against two types: HPV 16 and 18.

3. For HPV, the burden is based on the number of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV. The red line shows the burden for females, the blue line shows the burden for males.
4. Note that the y-axes are not the same for all diseases.
Sources: OSIRIS, NRLBM, sentinel laboratory surveillance, national cancer registry, PALGA, NIVEL-LINH

4.3 Burden of disease

In this section we present an update of the disease burden expressed in disability-adjusted life years (DALYs) of vaccine-preventable diseases in the period 2015–2019. We present the same estimates published in the 'State of infectious diseases in the Netherlands, 2019', in which more detailed information on the parameters used can be found [1]. Estimates for human papillomavirus (HPV) infection were derived from a separate analysis [2] and updated for more recent years using the Global Burden of Disease (GBD) 2010 life expectancy. Note that the calculation method used for HPV is not fully comparable to that for other diseases: instead of using the number of incident infections (which are unknown), the number of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV were used. All DALY estimates were rounded up or down: to three significant digits for numbers ≥10,000, to two significant digits for numbers between 10 and 10,000, and to one significant digit for numbers <10.

Table 3.1 shows the estimated DALYs per year in the period 2015–2019 and the DALYs per 100 infections in 2019 (a measure of the disease burden at individual patient level) in the Netherlands, with 95% uncertainty intervals. For diphtheria, poliomyelitis, rabies, rubella, and tetanus, the estimated disease burden in 2019 was zero because no cases were reported. For mumps, the disease burden in 2019 was estimated to be very low, while the highest burden was estimated for HPV infection, followed by invasive pneumococcal disease, pertussis, rotavirus infection, invasive *Haemophilus influenzae* disease, and invasive meningococcal disease.

The incidence of pertussis and rotavirus infection is known to surge every few years (Figure 3.1). For most diseases, the estimated burden in 2019 was comparable to the estimated burden in 2018. The burden for invasive pneumococcal and meningococcal disease was lower whereas the burden of HPV (for females), measles and pertussis was somewhat higher in 2019 compared with 2018. The burden for invasive meningococcal disease in 2019 was lower because of the considerable decline in the number of patients (from 103 reported cases in 2018 to 62 reported cases in 2019) caused by serogroup W (see also Chapter 7.6). The proportion of the burden due to serogroup W in the total burden of invasive meningococcal disease decreased from 42% in 2018 to 29% in 2019. For invasive pneumococcal disease, both the number of cases caused by vaccine types as well as non vaccine types decreased. The proportion of the burden due to vaccine types in the total burden of invasive pneumococcal disease decreased from 10% in 2018 to 4% in 2019. The higher burden of invasive pneumococcal disease in 2018 may be related to the severe influenza epidemic in that season. The higher measles burden was caused by an increase in measles incidence in 2019 compared to previous years, including a local measles outbreak in Urk.

It must be noted that the total disease burden for pneumococcal disease, meningococcal disease, and *Haemophilus influenzae* disease is higher than presented here because we limited our analyses to invasive disease. The disease burden related to hepatitis B virus infection has also been underestimated. Our analyses only reflect the (future) burden of new cases of hepatitis B virus infection in the period 2015–2019, which means that the disease burden of (chronic) hepatitis B cases infected prior to this period is not included.

4.4 Literature

4.1.1 *References*

1.* Lagerweij GR, Schimmer B, Mooij SH, Raven CFH, Schoffelen AF, de Gier B, et al. State of Infectious Diseases in the Netherlands, 2019. Bilthoven: National Institute for Public Health and the Environment (RIVM); 2020. RIVM report 2020-0048.
2.* McDonald SA, Qendri V, Berkhof J, de Melker HE, Bogaards JA. Disease burden of human papillomavirus infection in the Netherlands, 1989-2014: the gap between females and males is diminishing. Cancer Causes Control. 2017;28(3):203-14.

*RIVM publication

5. Adverse events

J.M. Kemmeren

5.1 Key Points

- In 2019, Lareb received 2,009 reports of a total of 7,378 adverse events following immunization (AEFIs). Compared to 2018, the number of reports increased by 32%, while the number of reported AEFIs increased by 42%. The increase in number of reports is mainly due to the catch-up campaign of MenACWY vaccination in adolescents. The number of reported AEFIs per report remained stable.
- No new signals of disturbing adverse events were found.

5.2 Tables and Figures

Table 5.1 Number of reports per dose and suspected vaccine(s) [1]

Vaccines	Total 2018	**Total 2019**	2m	3m	4m	5m	11m	14m	4yr	9yr	12-13yr	14-18yr	Pregnant women	Other/ Unknown
Vaxelis® + Synflorix®		**278**	139	50	37	22	23							7
Infanrix hexa® + Synflorix®	457	**192**	24	3	19	17	100							29
Vaxelis®		**99**	13	48	16	5								17
Synflorix®	9	**5**	1	2			1							1
Infanrix hexa®	118	**40**	4	12	5	2	4							13
MMRvaxPro® + Nimenrix®	173	**227**						216						11
MMRvaxPro®	16	**39**						13		3				23
MMRvaxPro® + NeisVac-C®	85													
NeisVac-C®	1													
Boostrix Polio®	326	**313**							307					6
Infanrixhexa® zonder Hib		**13**							9					4
MMRvaxPro® + Revaxis®	103	**118**								117				1
Revaxis®	7	**12**								8				4
Cervarix®	81	**104**									75	28		1
Nimenrix®	121	**520**						7				469		44
Boostrix®		**9**											9	
Other	22	**40**												40
Total 2019		**2009**	181	115	77	46	128	236	316	128	75	497	9	201
Total 2018	1519		187	61	108		170	263	326	110	65	62		167
Total 2017	1383		216	73	94		154	200	387	106	77			76
Total 2016	1483		174	60	95		126	171	572	84	146			55
Total 2015	1494		173	69	87		142	208	422	88	257			48
Total 2014	982		148	64	74		101	139	274	108	59			15
Total 2013	1212		217	118	75		118	133	335	92	82			42
Total 2012	1387		250	154	110		103	138	423	52	104			53
Total 2011	1103		212	154	86		105	129	280	51	51			35

Table 5.2 Reported severe adverse events per vaccination moment in 2019 [1]

	2m	3m	4m	5 m	11 m	14 m	4yr	9yr	12y r	14y r	Pregna nt wome n	Unknow n /other	Total
Rash, eczema	**10**	**8**	**9**	**4**	**8**	**115**	**14**	**21**	**3**	**24**	**0**	**30**	**246**
Respiratory symptoms, decreased consciousness	**25**	**10**	**13**	**4**	**6**	**7**	**5**	**14**	**8**	**45**	**0**	**12**	**149**
Collapse, (pre)syncope, drop attacks	3	2	2	0	0	1	2	13	7	34	0	3	67
Apnoea, dyspnoea, irregular breathing	10	4	5	3	6	6	3	1	1	11	0	6	56
Hypotonic-Hyporesponsive Episode (HHE)	8	3	5	1	0	0	0	0	0	0	0	2	19
Breath holding spells	3	1	0	0	0	0	0	0	0	0	0	0	4
Apparent Life Threatening Event (ALTE)	1	0	1	0	0	0	0	0	0	0	0	1	3
Extensive swelling of vaccinated limb (ELS)	**3**	**5**	**3**	**0**	**7**	**2**	**45**	**1**	**0**	**7**	**0**	**14**	**87**
Convulsions, epilepsy	**3**	**3**	**2**	**7**	**8**	**17**	**3**	**3**	**4**	**8**	**0**	**8**	**66**
(febrile) Convulsions, seizures	2	2	1	4	7	15	2	1	0	5	0	5	44
(febrile) Delirium	0	0	0	0	0	0	1	1	0	0	0	0	2
Epilepsy, status epilepticus	1	0	0	1	0	1	0	0	1	1	0	0	5
Ataxia, spasms, tics	0	1	1	2	1	1	0	1	3	2	0	3	15
Fever ≥40.5°C ≤42°C	**2**	**0**	**2**	**4**	**4**	**20**	**4**	**3**	**1**	**0**	**0**	**9**	**49**
Allergic reaction, anaphylaxis	**1**	**1**	**1**	**1**	**3**	**13**	**9**	**7**	**2**	**5**	**0**	**14**	**57**
Persistent crying	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2**
Skin discolouration	**10**	**7**	**4**	**3**	**1**	**1**	**1**	**0**	**0**	**1**	**0**	**0**	**28**
Abscess	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**
Injection site abscess	0	0	0	0	1	0	0	0	0	0	0	0	1
Lymph node abscess	0	0	0	0	0	0	0	0	0	0	0	0	0
Abscess of salivary gland	0	0	0	0	0	0	0	0	0	0	0	0	0
Immune mediated disorders	**0**	**0**	**0**	**0**	**0**	**2**	**1**	**0**	**0**	**2**	**0**	**0**	**5**
Diabetes Mellitus	0	0	0	0	0	0	1	0	0	1	0	0	2
Acute haemorrhagic oedema of infancy	0	0	0	0	0	0	0	0	0	0	0	0	0
Immune thrombocytopenic purpura (ITP)	0	0	0	0	0	1	0	0	0	0	0	0	1
Kawasaki's disease	0	0	0	0	0	1	0	0	0	0	0	0	1
Juvenile idiopathic arthritis	0	0	0	0	0	0	0	0	0	0	0	0	0
Dehydration	**0**	**0**	**0**	**0**	**1**	**3**	**0**	**0**	**0**	**0**	**0**	**0**	**4**
Death*	**2**	**0**	**1**	**0**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**5**
SIDS	1	0	1	0	0	0	0	0	0	0	0	0	2
Other	1	0	0	0	1	1	0	0	0	0	0	0	3
Encephalitis, meningitis	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**4**	**0**	**1**	**6**
Postural orthostatic tachycardia syndrome	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Vaccine failure	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

Chronic fatigue	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Venous thrombosis	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Chronic arthritis	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Complex regional pain syndrome (CRPS)	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

* For a full descriptions of the causes of death: see yearly report of Lareb [1]

5.3 Spontaneous Reporting System

5.3.1 *Reports*

The enhanced passive surveillance system managed by the National Centre for Pharmacovigilance Lareb receives AEFI reports for all vaccines covered by the NIP. In 2019, Lareb received 2,009 reports with a total of 7,378 AEFIs (Table 5.1) [1]. Compared to 2018, the number of received reports increased by 32.3% (1,519 in 2018), while the number of reported AEFIs increased by 41.7% (5,208 in 2018). The increase in the number of reports received can be explained by the catch-up campaign of the MenACWY vaccination in adolescents of 14-18 years of age in 2019. Most reported AEFIs were injection site reactions (n=2,063), fever (n=821), headache (n=295, from which 197 after the MenACWY vaccination during the catch-up campaign) and crying (n=251). Of the reports, 95 (4.7%) were classified as serious.
The number of reports per dose and vaccine are mostly within the range of the last eight years (see Table 5.1), although there appears to be a shift in number of reports after vaccination in the first year of life. This may be related to the introduction of maternal vaccination in the Netherlands in 2019 and a change in DKTP-Hib-hepB vaccine used in the NIP [1].
For infants aged 11 months, the number of reports decreased for the first year since 2015. The number of reports in infants aged 14 months is also decreased. The decrease in the number of reports after administration of DTP-IPV at the age of 4 years which started in 2017 (n=387; n=326 in 2018) continued in 2019 (n=316), whereas an increasing trend is seen after the vaccination at 9 years of age. The decrease of number of notifications received after the administration of the HPV vaccine seems to have to stopped in 2019 (see Table 5.1). Twenty-eight reports were received after HPV vaccination in girls of 14-18 years of age. Normally HPV vaccination takes place at the age of 12 years. As a result of the invitations for the MenACWY vaccination of the 14-18 year olds, some youth health care organizations invited girls to still get the HPV vaccination.
The increasing trend in number of reports after vaccination on a different or unknown vaccination moment which started in 2017 (n=76; n=167 in 2018), continued in 2019 (n=201). This was mainly observed for vaccinations in the first years of life, and after vaccination with Nimenrix (n=44) which frequently is administered outside the NIP and catch-up campaign. Reasons for the increasing trend for the other vaccines are unknown
The number of reported AEFIs per report remained stable (3.7% in 2019 vs 3,9% and 3.4% in 2017 and 2018, respectively).

Table 5.2 summarizes severe adverse events per vaccination moment as reported to Lareb. These events are included because of their severity and their known or perceived relation with vaccination. In general, the

spectrum of reported AEFIs is mostly in line with previous years. The decline in reports of extensive limb swelling among 4-year-olds (n=59 in 2017 and n=21 in 2018) did not continue in 2019 (n=45). Furthermore, an increase in notifications of rash was seen after the vaccination at the age of 14 months (n=94 in 2017, n=95 in 2018 vs n=115 in 2019). The introduction of Nimenrix in spring 2018 does not appear to be responsible for this increase as no increase was observed in 2018. The increase may be a result of natural variation over the years, which will be monitored.
No reports of postural orthostatic tachycardia syndrome (POTS) and chronic fatigue syndrome (CFS) after HPV vaccination were received. Fatigue after HPV vaccination was reported 13 times, which is comparable to 2018 (n=18) and considerably less compared to 2017 (n=30).
Overall, no new signals of disturbing adverse events were found.

5.3.2 *Signals*

5.3.2.1 Lymphadenopathy, urticaria and febrile seizures after vaccination with Nimenrix®

In 2019, Lareb published three signals related to reports about lymphadenopathy, urticaria and febrile seizures, respectively, after vaccination with Nimenrix® [2-4]. Analyzes of these reports show that swollen and sometimes painful lymph nodes and febrile seizures are AEFIs that may occur. Febrile seizures have only been reported in the children who received the vaccination at 14 months of age. The appearance of an itchy rash and urticaria may also be a side effect. This AEFI may be related to a hypersensitivity reaction. These AEFIs are known side effects of Nimenrix®, but are not yet explicitly included in the package leaflet of this vaccine.

5.4 **International Developments**

5.4.1 *Non vaccine-specific adverse events*

The growing number of available vaccines that can be potentially co-administered makes the assessment of the safety of vaccine co-administration increasingly relevant but complex. A systematic review included fifty studies which compared co-administered vaccines versus the same vaccines administered separately. The most frequently studied vaccines included quadrivalent meningococcal conjugate (MenACWY) vaccine, diphtheria and tetanus toxoids and acellular pertussis (DTaP) or tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccines, diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B, inactivated poliovirus and *Haemophilus influenzae* type b conjugate (DTaP-HepB-IPV/Hib) vaccine, measles, mumps, and rubella (MMR) vaccine, and pneumococcal conjugate 7-valent (PCV7) or 13-valent (PCV13) vaccines. Of this, 16% (n = 8) of the studies reported significantly more adverse events following immunization (AEFI) while in 10% (n=5) significantly fewer adverse events were found in the co-administration groups. Statistically significant differences between co-administration and separate administration were found for 16 adverse events, for 11 different vaccine co-administrations. This study indicated that differences in safety of vaccine co-administrations compared to separate vaccine administrations may exist, particularly for more common, less severe AEFI. However, the authors concluded that the safety of vaccine co-administrations compared to separate vaccine

administrations is inconclusive and there is a paucity of large post-licensure studies addressing this issue [5].

5.4.2 *Vaccines targeting diseases included in the current NIP*

5.4.2.1 MMR/MMRV

Several studies demonstrated the safety of the MMR/MMRV vaccine [6-8], although more evidence is needed to assess whether the protective effect of MMR/MMRV could wane with time since immunization [6]. An early MMR dose in infants younger than 9 months or 2-dose measles schedule at 6 and 12 months also showed to be safe [9, 10]. Live attenuated vaccine safety was demonstrated in HIV infected children (MMR) [11] and adult patients receiving hematopoetic stem cell transplantation (MMRV) [12]. An increase in the risk for ITP was observed in children receiving the varicella and MMR vaccines concomitantly (IRR 1.70; 95% 1.02-1.18) [13], but erythema multiforme, Steven Johnson syndrome, and toxic epidermal necrolysis were rarely reported after childhood vaccines (e.g. MMR vaccination) [14]. One case report was published about a 4-years-old boy who was admitted with rash and documented disseminated varicella infection 5 weeks after MMRV vaccination [15]. This illustrates what is still unknown about the risk-to-benefit ratio of live viral vaccination in any individual transplant recipient.
A systematic review of pregnancy related AEs following rubella vaccination did not demonstrate an evidence that congenital rubella syndrome is caused by rubella-containing vaccines. However, transplacental vaccine virus infection can occur [16], although the risk/benefit balance is in favor of vaccination. The data confirmed that inadvertent vaccination during pregnancy was not an indication for termination of pregnancy.
Several studies demonstrated that co-administration of MMRV and MenC conjugate vaccines did not have a negative impact on the safety of either vaccines, as concluded in a review by Bonanni [17]. A preclinical study of safety and immunogenicity of combined rubella and HPV vaccines in mice showed that a good safety profile of this combined vaccine [18]. Such a vaccine can be of great value to females above 20 years in low income countries to increase vaccine uptake after clinical testing.

5.4.2.2 Pneumococcal vaccine

A phase II trial showed the safety of a novel PCV12 conjugate vaccine [19]; the overall incidence of solicited systemic adverse events was even lower than in the comparator PCV13 group. A good safety profile was also found in several studies to the safety of PCV13 [20, 21], even in HIV infected adults [22] and patients with monoclonal gammopathy of undetermined significance [23]. Furthermore, no evidence was found of an association between PCV13 vaccination and Kawasaki disease onset in the 4 weeks after vaccination nor of an elevated risk extending or concentrated somewhat beyond 4 weeks [24]. A phase I study showed that vaccination with PCV20 was well tolerated in healthy adults. A study with PPV23 vaccine confirmed the safety of this vaccine in elderly people with chronic lung disease [25], although self-limited local and systemic reactions were more frequent after the second and third vaccinations than after the first vaccination. One review described that PCVs are safe for use in nephrotic patients [26].

Two phase I studies were conducted to assess the safety of novel pneumococcal vaccines that are affordable for resource-limited settings. Both investigational vaccines (wSp and SIIPL-PCV) were well-tolerated and had an acceptable safety profile [27, 28]. In a phase IIb trial a novel dPly/PhtD vaccine was well tolerated in Native American infants [29].

5.4.2.3 Meningococcal ACWY vaccine

Three prelicensure trials were published about the safety of MenACWY-TT. All showed a good reactogenicity profile in adolescents and/or adults [30-32]. The safety profile of this vaccine was also demonstrated regardless of age, primary versus booster vaccination, concomitant vaccine administration or in children primed with MenC vaccine [33-35]. The safety of MenACWY-CRM vaccine in all age groups was also demonstrated in several studies [36-38]. One study assessed the baseline prevalence estimates of spontaneous abortions, preterm births, low weight births, and major congenital malformations among women inadvertently exposed to MenACWY-CRM during pregnancy period [39]. These estimates appeared to be comparable with US background prevalence estimates.
The concomitant administration of meningococcal vaccines with other vaccines in adolescents and adults was reviewed by Alderver et al [40]. In general, data suggest that these vaccines can be safely co-administered with other vaccines.
In an exploratory study the safety of 1 and 2 doses of an MenAC-TT vaccine in toddlers was demonstrated [41]. A review about the safety profile of a MenA vaccine showed that the incidence of AEs after MenA vaccination was for lower in campaigns then in clinical trial studies [42]. This systematic review highlights the magnitude of the difference between IR of AEFI as evaluated in the controlled setting of clinical trials and more pragmatic approach of mass vaccination campaigns.

5.4.2.4 DTaP-IPV-HBV-Hib

Two studies showed the safety of pentavalent DTwP-HBV-Hib combination vaccine [43, 44] and one study demonstrated the safety of DTaP-IPV/Hib vaccine [45]. Another study showed the safety profile of a fully liquid, ready to use, hexavalent vaccine, which was similar to that of several approved vaccines [46].
Several studies were published concerning the safety of maternal pertussis vaccination. In all these studies, no safety issues were encountered for mother and/or child [47-50]. One of the studies found an association between infant exposure to Tdap during pregnancy an ankyloglossia and neonatal erythema toxicum diagnosis [47]. Both were supposed to be a result of residual confounding, or spurious associations to the large number of endpoints. Four overviews confirmed the safety of maternal Tdap immunization [51-54], although one advised to optimize the timing of vaccination in pregnancy. There is currently no evidence of an association between vaccination during pregnancy and neonatal seizures [54]. There is also no evidence for higher frequency of clinically relevant sequelae due to an increased risk of fever and chorioamnionitis after maternal pertussis vaccination [51].

5.4.2.5 HPV

Several studies and reviews demonstrated the safety of HVP vaccines [55-57]. No evidence of increased infertility [58], CRPS, chronic fatigue, POTS or other forms of dysautonomia [59], Guillain-Barre syndrome [60], autoimmune and other rare diseases [61] were published. The concomitant administration of other vaccines along with HPV vaccines was acceptable [62] and inadvertent HPV vaccination during pregnancy was not associated with significantly greater risks of adverse pregnancy outcomes [63].Two studies proved that HPV vaccine is safe in HIV infected people [64, 65]. Another study revealed a different distribution pattern of AEs across gender and age subgroups and correlated patterns across various AEs after HPV vaccination [66]. However, further clinical studies are needed to understand the heterogeneity of these AEs and the biological pathways among the statistically correlated AEs.
A descriptive study that AEs-reporting rates for HPV immunization have decreased considerably, perhaps by a reduction and stabilization of reporting over time or decreased media attention [67]. A study in Denmark showed that despite an official aim of homogenous case management, reporting of suspected AEs was incomplete with large regional difference [68]. This observation represents an important caveat in interpreting data from AEs reporting, in particular wen these data are used for research or policymaking.

5.4.2.5.1 2vHPV, 4vHPV, 9vHPV vaccines
Results from studies on the safety of 2vHPV did not reveal new or unexpected safety concerns in female and/or male adolescents [69-71], and in children of 4-6 years of age [72]. Also 4vHPV vaccine showed to be well-tolerated without new safety signals [73, 74], even by concomitant administration of 4vHPV, Tdap and MenACWY-CRM in adolescents [75]. The findings of a phase I study suggest that 4vHPV vaccination may be safely administered to women post-allogeneic transplant to potentially reduce HPV infection and related neoplasia [76]. Five studies reported no new or unexpected safety concerns or reporting patterns of 9vHPV with clinically important AEs were detected [77-81].

5.4.2.5.2 New vaccines
A phase III clinical trial was conducted to evaluate the efficacy, safety, and immunogenicity of a novel Escherichia coli-produced bivalent HPV-16/18 vaccine [82]. In the per-protocol cohort, the side effects were mild and no vaccine-related serious adverse events were noted. This novel vaccine showed to be well tolerated.

5.4.3 *Other potential future target diseases*

5.4.3.1 Meningococcal B

In Canada, active safety surveillance identified an unexpected increase in nephrotic syndrome incidence following 4CMenB vaccination [83]. The greater risk in vaccines had wide confidence intervals with the lower limit including or just above the null value (i.e. RR 8.3; 95% CI when compared to pre-vaccination period and RR 3.6; 95% CI 0.7-11.8 when compared with region without mass vaccination). The temporal association with vaccination may be explained by other causes and/or chance clustering of a rare event unrelated to vaccination. Another study found that 4cMenB is associated with AEs (temperature >37.5 °C, needed partial septic screens, needed intravenous antibiotics) in

hospitalized preterm infants [84]. Prophylactic paracetamol administration attenuates this. Nicolosi et al demonstrated that 4CMenB is almost well tolerated, with a low incidence of severe AEs. The only AEFI that has been perceived as severe by a significant number of parents and caregivers was the refusal to move the extremity (described as severe in 12.1% of all the vaccinated children). They also showed that the occurrence of AEs is similar within healthy children and children with chronical medical conditions [85]. A randomized trial in Canada of 2 schedules of 4CMenB vaccine in adolescents and young adults showed that the rate of unsolicited AEs did not differ by dosing schedule or dose. One participant had a serious AE unrelated to vaccination [86]. After more than 3 million 4CMenB doses administered to infants, no safety concerns have been identified in the UK [87].

5.4.3.2 Varicella

The safety of live attenuated varicella vaccine was demonstrated in a trial in China [88]. A comprehensive 22-year review confirms the overall safety for this vaccine, with no new safety concerns identified [89]. AEs occurred with similar frequency and severity between HIV-unexposed and HIV-exposed uninfected children, except for more systemic AEs after varicella vaccination in HIV-unexposed than in HIV-exposed uninfected children (57% vs 29%; p=0.007) [90]. The underlying reason for this difference remains unclear. In Taiwan, a small risk of incidental pneumonia associated with varicella vaccine in the 6th week after immunization was detected (IRR 1.10; 95%CI 1.02-1.18) [13]. There was no increase in the risk of other pre-specified adverse events (i.e. ITP, meningitis, encephalitis, and ischemic stroke). Harrington presented two adolescents with reactivated vaccine Oka meningitis, one immunocompetent and one immunocompromised, both of whom received 2 doses of varicella vaccine many years before as children [91]. This finding of the potential of vaccine Oka varicella to reactivate may be important in future diagnosis and care of patients with meningitis and encephalitis.
In a double-blind, randomized, multicenter study, the safety and tolerability of a refrigerator-stable varicella vaccine was similar to that of the frozen formulation [92].

5.4.3.3 Herpes Zoster

No safety concerns were identified for live-attenuated herpes zoster vaccination, even in patients with rheumatoid arthritis, in patients with systemic lupus erythematosus, or patients with solid tumour malignancies receiving chemotherapy or other underlying chronic diseases [93-97]. A methodological study to test the self-controlled tree-temporal scan statistic in older adults also demonstrated consistent results with local-site reactions and other known, generally mild, vaccine-associated AEs and a favorable safety profile for live-attenuated herpes zoster vaccine [98].
Recombinant zoster vaccine is associated with local and systemic reactions that is significantly greater than observed with commonly used vaccines [99]. Several studies confirmed these findings although no safety concerns were identified [100-102], even when co-administered with Tdap [103]. The safety profile of recombinant zoster vaccine was not impacted when given to adults who received previously live-attenuated herpes zoster vaccine [104]. In addition, no safety concerns

arose after recombinant zoster vaccination in patients with inflammatory bowel disease and in chronically immunosuppressed adults [105-107]. A Cochrane Review assessed the safety of vaccination for preventing herpes zoster in older adults [108]. In this review it was concluded that both live-attenuated herpes zoster vaccines and recombinant zoster vaccines produce systemic and injection site adverse events of mild to moderate intensity.

5.4.3.4 Hepatitis A

In Australia, a combined hepatitis A and typhoid vaccine is available, but licensed for use from age 16 years. This year, a study showed that this vaccine is also well tolerated in children aged 2-16 years and the risk of adverse events is similar to those receiving concurrent monovalent vaccines [109]. Another study showed that hepatitis A vaccination during pregnancy was not associated with an increased risk for a range of AEs examined among pregnancies resulting in live births. However, an identified association between maternal hepatitis A and small-for-gestational age infant outcomes, while likely due to unmeasured confounding, warrants further exploration [110].

5.4.3.5 Hepatitis B

Hepatitis B vaccination showed to be safe and well tolerated in patients with rheumatoid arthritis, patients with type 2 diabetes, patients with chronic kidney disease not yet on maintenance dialysis, and HIV infected adults [111-114]. Stowe et al evaluated the epidemiological evidence for a relationship between vaccination and neurological diseases. They found no evidence for the hypothesized relationship between multiple sclerosis and hepatitis B vaccination [60].

5.4.3.6 Rotavirus

Several studies showed an increased risk for intussusception after rotavirus vaccination [115-118]. However, the overall risk for intussusception in the first year of life seems not to be increased or even decreased [115, 117] and a nonsignificant decrease in intussusception was found in the US in fully rotavirus vaccinated children followed up to the age of 2 years [119]. In Ireland, no increase in the national crude incidence rate of intussusception was observed after inclusion of rotavirus vaccination in the NIP [120] and the risk of intussusception in the 21 days after the first or second dose of monovalent rotavirus vaccination was not higher than the background risk among South Africa infants [121]. These findings confirm the conclusion of a study in New Zealand, where no change in the overall incidence of intussusception or clear change in patterns of cases was seen, although intussusception cases did occur within risk period immediately post vaccine [122]. An overview of several quantitative benefit-risk models showed across all included studies, the benefits of rotavirus vaccination that largely exceed the increased risk of intussusception [123]. A study in LMICs found a favorable benefit-risk profile for rotavirus vaccines which caused fewer excess intussusception deaths than the schedules currently recommended by WHO [124]. Results of a systematic review and meta-analysis suggest that monovalent, pentavalent, monovalent human-bovine, oral bovine pentavalent, and human neonatal rotavirus vaccination was not associated with an elevated risk of intussusception among neonates or infants [125]. However, this meta-analyses included

only randomized clinical trials which are inadequate to identify a potential increased risk of rare adverse events such as intussusception [126].
No association was found for rotavirus vaccination and Kawasaki disease [127] and for type 1 diabetes in children [128]. A review concluded that, although data were limited, co-administration of rotavirus and meningococcal vaccines does not appear to interfere with the safety of rotavirus vaccines [129].
New vaccines such as a heat-stable rotavirus vaccine and the trivalent P2-VP8 vaccine were shown to be well-tolerated [130, 131].

5.5 Literature

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*RIVM publication.

6. NIP-wide research topics

M. Middeldorp

6.1 Key points

- Following implementation of Dutch COVID-19 response measures, the reported incidence of pertussis, invasive pneumococcal disease (IPD), invasive meningococcal disease (IMD), and mumps has decreased.

6.2 Impact of the COVID-19 pandemic on incidence of vaccine preventable diseases in the Netherlands

The reported incidence of pertussis, invasive pneumococcal disease (IPD), invasive meningococcal disease (IMD), and mumps decreased after the implementation of the Dutch COVID-19 response measures. The most likely reason for the reduced incidence of several VPD is reduced transmission as result of social distancing measures and school closure [1]. However, factors like changed healthcare seeking behaviour, diagnostics capacity, and reporting delays may have contributed [2]. The findings suggest that, based on the magnitude of the effects and the timing, it is very likely the measurements initiated in response to the pandemic have reduced the true incidence of several VPDs.

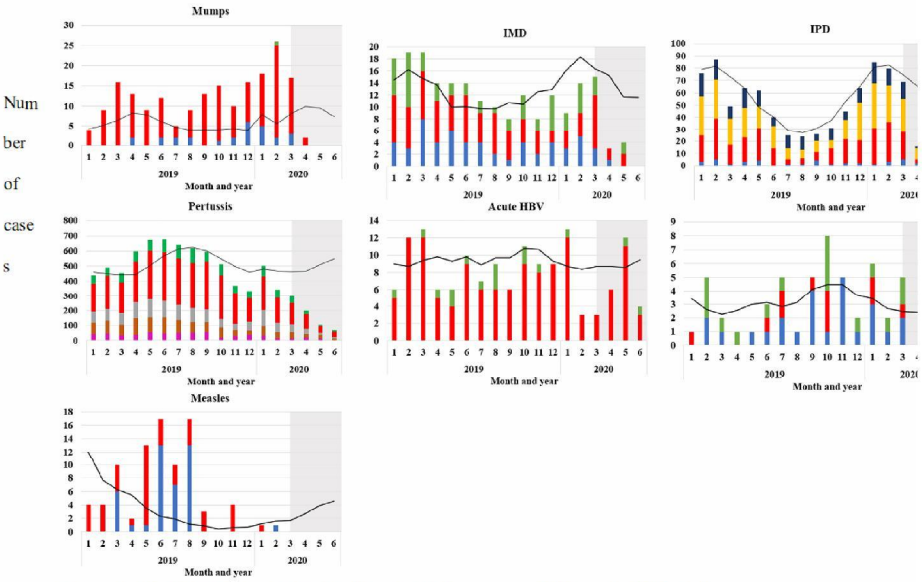

Figure 1. Number of cases per calendar month for mumps, IMD, acute HBV, and Hib among <18, 18-64 and 65+ year-olds, and number of cases for IPD among <18, 18-64, 65-79, and 80+ year-olds in the sentinel surveillance covering 25%

of the Dutch population, and number of cases per month for pertussis among <5, 5-11, 12-18, 18-64, and 65+ year-olds from January 2019 to June 2020 relative to the 5-year moving average. Nationwide control measures in view of the COVID-19 pandemic were taken on 15th of March and are shaded in the figure. From mid-May, some measures were relaxed in the Netherlands.

6.3 Literature

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7. Current National Immunisation Programme

7.1 Diphtheria

N.A.T. van der Maas, F.A.G. Reubsaet, G.A.M. Berbers, D.W. Notermans

7.1.1 *Key points*

- In 2019, one possible diphtheria case was reported with unknown vaccination history. Although clinical signs were very suspicious for diphtheria and patient received diphtheria antitoxin as treatment, no Corynebacterium was found.
- In 2020, until June 1st, no diphtheria cases were notified
- A European serosurveillance study showed that a substantial part of 40-60-year-olds had non-protective DT levels. Levels <0.01 IU/ml varied between 4% and 43%. For 0.1 IU/ml, these percentages varied from 23% up to around 80%. The percentage unprotected in the Netherlands was 12.8% (<0.01 IU/ml) and 57.5% (<0.1 IU/ml).

7.1.2 *Tables and figures*

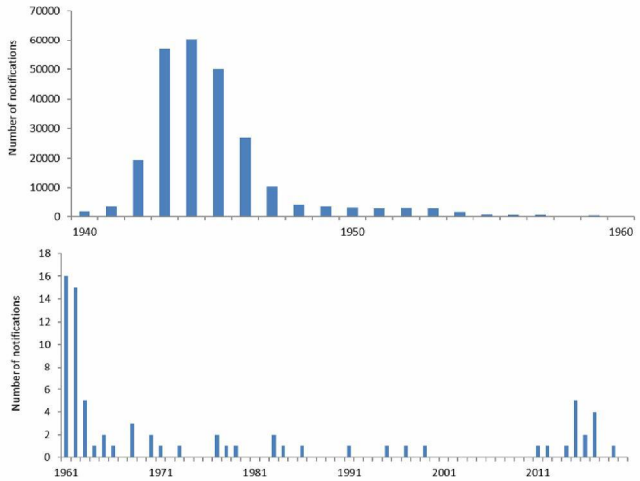


Figure 7.1.1 Diphtheria notifications per year for 1940-1960 (upper part) and 1961-2020(lower part)*

*notifications up to June 2020 are included

Table 7.1.1 Laboratory results of confirmation testing of Corynebacterium diphtheriae and C. ulcerans at RIVM for 2016-2020. Date delivery at the laboratory is used for year of classification.*

	Corynebacterium diphtheriae				*Corynebacterium ulcerans*			
	PCR negative	PCR positive	Elek Positive	Elek Non-conclusive	PCR negative	PCR positive	Elek Positive	Elek non-conclusive
2016	12	1	1	NA	2	1	NA	1
2017	9	1	0	0	0	2	NA	2
2018	7	0	0	0	1	2	1	1
2019	7	0	NA	NA	8	0	NA	NA
2020*	2	0	NA	NA	2	0	NA	NA

*up to June 1st, 2020
NA= not applicable

7.1.3 *Epidemiology*

In 2019, one possible case of diphtheria was reported (Figure 7.1.1). It concerned a man with clinical signs of respiratory diphtheria born in 1980 and with unknown vaccination history. De patient received anti diphtheria toxin. However, no Corynebacterium was found. In 2020, up to June 1st, no cases of diphtheria were notified.

7.1.4 *Pathogen*

In 2019, the RIVM received fifteen *C. diphtheria* or *C. ulcerans* strains, of all were from cutaneous samples except one sample from the nose and one case of chronic sinusitis. In 2020 up to June 1, the RIVM received four *C. diphtheria* or *C. ulcerans* strains from cutaneous samples. All strains were PCR negative.
See table 7.1.1 for details on laboratory results for the respective strains.

7.1.5 *International developments*

Within the framework of the EUPertstrain group, a collaboration between European experts on whooping cough, a seroprevalence study in European countries for pertussis, diphtheria and tetanus antibody levels in the 40-60 years age groups has been conducted by the RIVM and funded by ECDC. 18 European countries have participated and collected the requested sera (around 500). Measurement of the antibody levels against pertussis toxin, diphtheria toxoid and tetanus toxin with the MIA has been completed last year establishing a final database of around 30,000 results.
For diphtheria the prevalence of protective levels of anti-DT IgG antibodies seems quite alarming all over Europe with proportions of participants with DT levels <0.01 IU/ml (basic immunity) varying between 4% (Finland) and 43% (Greece). For the more reliable protective level of 0.1 IU/ml, these percentages vary from 23% for Finland up to around 80% for Greece, Ireland, Romania and the UK

leaving the majority of the 40-60 year age cohorts in Europe without protective immunity against diphtheria (manuscript submitted [1]). The percentage unprotected in the Netherlands was 12.8% (<0.01 IU/ml) and 57.5% (<0.1 IU/ml).

7.1.6 *Literature*

1. G. Berbers, P. van Gageldonk, J. van de Kassteele, U. Wiedermann, I. Desombere et al. Widespread ciriculation of pertussis and poor protection against diphtheria among middle-aged adults in 18 European countries. Nature research 2020, Preprint 2020. DOI 10.21203/rs-35858/v1.

7.2 *Haemophilus influenzae* disease

M.J. Knol, W. Freudenburg-de Graaf, R. Mariman, G. den Hartog, H.E. de Melker, N.M. van Sorge

7.2.1 *Key points*

- In 2019, the number of cases of *Haemophilus influenzae* type b (Hib) disease was similar to 2018 (39 vs 43 cases). Up to May 2020, 16 Hib cases have been reported, somewhat more than in the same period in 2019 (n=10) but similar to 2018 (n=17).
- In 2019, the incidence of Hib disease was highest among children under 5 years old (2.0 per 100,000). After an increasing trend in incidence observed from 2011 to 2016, the incidence stabilized in the period 2017-2019.
- There were 19 Hib cases in vaccine-eligible children in 2019, of which nine were sufficiently vaccinated, resulting in a Hib vaccine effectiveness estimate of 93%, similar to previous years.
- In 2019, a similar number of cases of non-typable Hi (NTHi) disease were reported as in 2018 (165 vs. 167), suggesting a stabilization of NTHi disease.
- No rise was observed in Hi due to other serotypes.

7.2.2 *Figures*

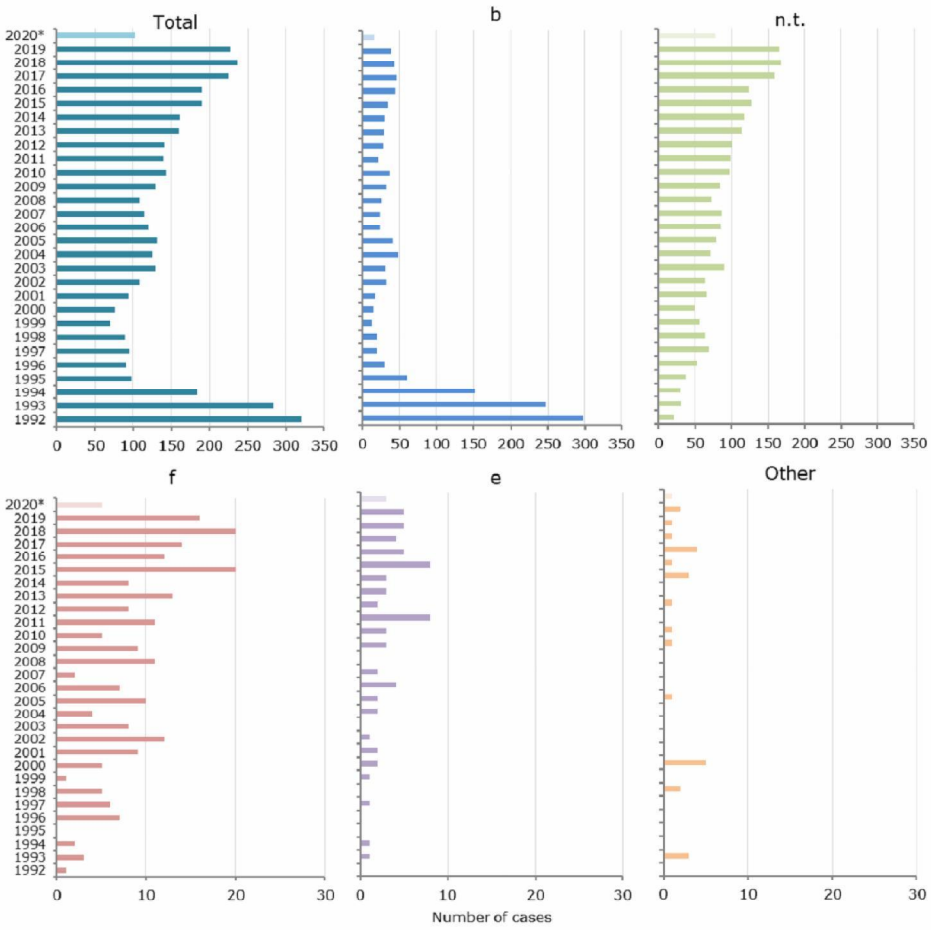


Figure 7.2.1 Number of Haemophilus influenzae cases per serotype, 1992-2020 (*up to May). Note: 'Other' category includes serotype a and serotype d*

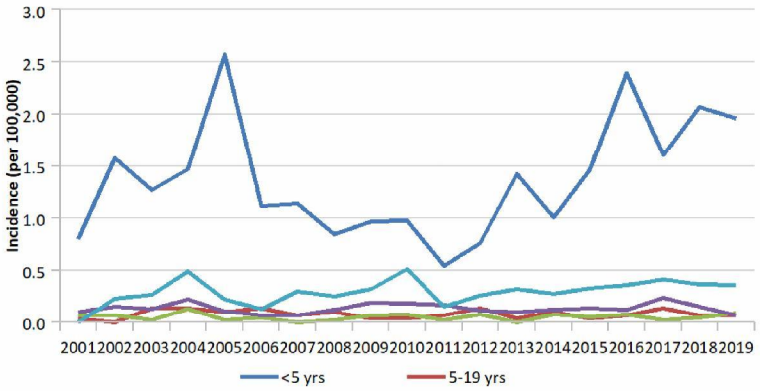


Figure 7.2.2 Age-specific incidence of Haemophilus influenzae type b (Hib) disease, 2001-2019

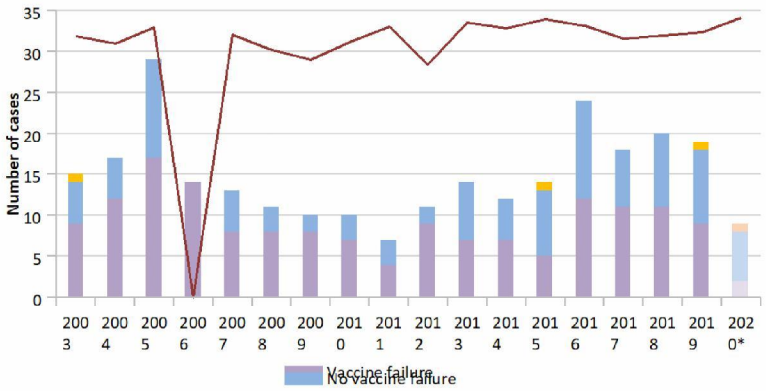


Figure 7.2.3 Number of Haemophilus influenzae type b (Hib) cases in cohorts eligible for vaccination (i.e. born after 1 April 1993) by vaccination status and estimated vaccine effectiveness, 2003-2020 (*up to May). Note: in 2006, VE could not be estimated because 100% of the cases were vaccinated.*

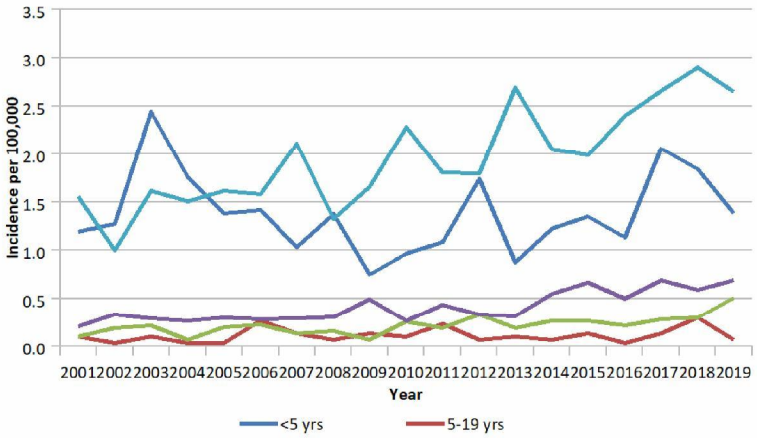


Figure 7.2.4 Age-specific incidence of non-typable Haemophilus influenzae disease, 2001-2019

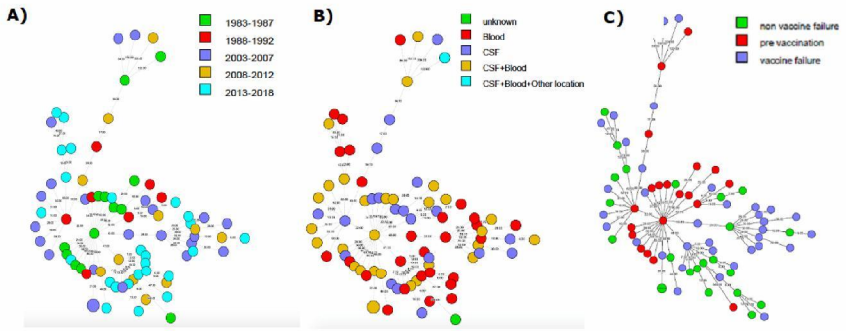


Figure 7.2.5. Genetic relationship between 80 clinical isolates based on cgMLST. Each node of the minimum spanning tree based on cgMLST represents a single Hib isolate. The length of the lines between isolates represents the number of different genes. No clustering of strains by year of isolation (A), invasiveness (B), or vaccination status (C) can be observed.

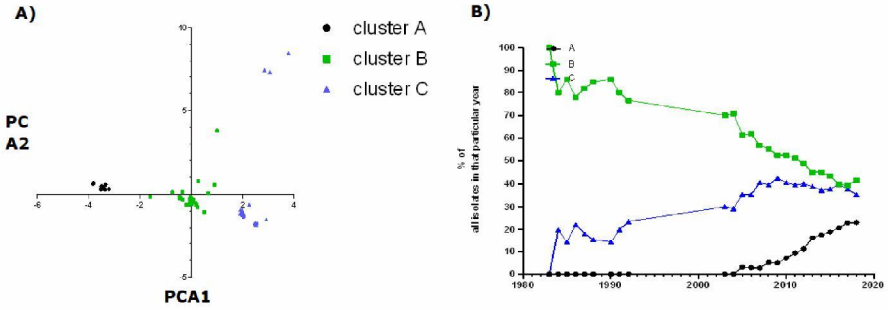


Figure 7.2.6 (A) Unsupervised principal component analysis (PCA) on the total cgMLST (1,738 genes) of 65 isolates with the dominant Sequence Type 6 revealed 3 clusters along components 1 and 2. (B) Relative contribution of each cluster to the total number of isolates analysed in a particular year.

7.2.3 *Epidemiology*

7.2.3.1 Hib disease

7.2.3.1.1 Incidence

Between 2011 and 2016, the number of Hib cases rose from 22 to 44. Between 2017 and 2019, the number of Hib cases stabilized and in 2019 39 cases were observed (incidence: 0.23 per 100,000) (Figure 7.2.1). The incidence was highest in children <5 years old (2.0 per 100,000; n=17) and has been stable in this age group since 2016 (Figure 7.2.2). Up to May 2020, 16 Hib cases have been reported, somewhat more than in the same period in 2019 (n=10) but similar to 2018 (n=17). The outcome status was known for 36 and 13 cases in 2019 and 2020, respectively. Of these, two patients of 65 years or older died in 2019.

7.2.3.1.2 Vaccinated cases

In 2019 and 2020 (up to May), 19 and nine Hib cases were reported among cohorts eligible for vaccination, respectively (Figure 7.2.3). Fourteen (50%) of these cases were unvaccinated (nine in 2019, five in 2020), one case was vaccinated once (in 2020) and eleven (42%) were sufficiently vaccinated (i.e. received at least two vaccinations with at least two weeks between the second vaccination and date of diagnosis; nine in 2019 and two in 2020); vaccination status was unknown in two cases. The unvaccinated children were between zero and 17 months old. Most vaccinated cases (seven in 2019 and one in 2020) were younger than five years old. Three (27%) of the vaccinated cases had a known immune disorder.

7.2.3.1.3 Vaccine effectiveness

The estimated vaccine effectiveness (VE) of Hib vaccination using the 'screening method' (see Appendix 1 section 1.1.2.3) was 93% (95%CI

81-97%) in 2019 (Figure 7.2.3). The overall VE for 2003-2020 was 92% (95%CI 90-94%).

7.2.3.2 Non-typable Hi (NTHi) disease

In 2019, 165 cases of NTHi were reported. This was similar to 2018 (167 cases) and 2017 (159 cases), suggesting a stabilization in NTHi disease (Figure 7.2.1). Up to May 2020, 77 cases have been reported, which is lower than the number reported in the same period in 2019 (91 cases), which may be caused by the COVID-19 measures (e.g. social distancing and increased hygiene) which started half of March; especially in April and May 2020 the number of cases was lower than the average in that period in the last five years. In 2019, the incidence was still highest among persons aged 65 and over (2.7 per 100,000; n=88) and children aged under five years (1.4 per 100,000; n=12) (Figure 7.2.4).

7.2.3.3 Disease due to other Hi serotypes

In 2019, five Hi cases with serotype e (Hie) were reported, similar to previous years (Figure 7.2.1). Up to May 2020, three Hie cases have been reported. In 2019, 16 cases of Hif were reported (Figure 7.2.1). Up to May 2020, five Hif cases have been reported. In 2019 and 2020 (up to May), three Hi cases with serotype a have been reported.

7.2.4 *Pathogen*

There are no indications that the pathogenicity of Hib has changed.

7.2.5 *Current/ongoing research at RIVM*

In 2019, we conducted a study that aimed to elucidate thus far unexplained changes in epidemiology of invasive Hib in the Netherlands by genotypic characterization of clinical isolates. Therefore, we applied Whole-Genome-Sequencing (WGS) to 80 Hib strains isolated from children <5 years diagnosed with invasive Hib disease. From the collection of the Netherlands Reference Laboratory for Bacterial Meningitis, 20 strains were randomly selected from the pre-vaccine era (1986-1992) and 60 strains, from both vaccinated and unvaccinated children, represented the vaccine era (2003-2018). A core-genome multi locus sequence typing (cgMLST) scheme, using an in-house scheme consisting of 1738 genes, was used to infer genetic relationships between the isolates. A minimum spanning tree based on cgMLST, showed substantial genetic variation within the Dutch Hib population with an average distance of 35 genes between two neighbouring isolates (range 1–148 genes). There was no clustering in the cgMLST observed based on year of isolation, age, vaccination status, or invasiveness (Figure 7.2.5).
However, in depth analysis of the dominant Sequence Type (ST) 6 (65 out of 80 strains) by principal component analysis (PCA) on the binary transformed cgMLST data revealed three distinct clusters of isolates (Figure 7.2.6A). One cluster that appeared after the introduction of the vaccine is gradually increasing and now comprises one-third of all clinical isolates (Figure 7.2.6B).
Statistical analysis between the three clusters identified 87 genes that were significantly different in any of the comparisons. Among these, genes encoding Immunoglobulin A1 protease autotransporter and Outer membrane protein P1 might be of interest in the context of disease. The preliminary data suggest that the increase in cases up to 2016 might be

caused by expansion of a more successful genotypical Hib cluster. Ongoing research focuses on the genes that drive these clusters.

Data from two population-based cross-sectional serosurveillance studies were used (Pienter-2 study in 2006-2007 and Pienter-1 study in 1995-1996) to assess and compare the concentration of antibodies to the capsular polysaccharide of Hib (1). Post-primary vaccination serum samples from children aged 6–11 months from the Pienter-2 study contained approximately 4-fold lower anti-Hib antibody concentrations than samples from children from the Pienter-1 study. No such difference was found in post-booster samples from children older than 11 months of age. In Pienter-2, the proportion of children aged 6–11 months with anti-Hib antibody concentrations below the putative protective concentration of 0.15 µg/mL was 30%, which was significantly higher than in the Pienter-1 study (12%). Fewer children in the Pienter-2 group developed antibodies able to kill Hib in a serum bactericidal assay compared to the Pienter-1 children. The cause of the lagged response in Pienter-2 children remains uncertain, but lack of natural boosting, interference by the acellular pertussis vaccine, the use of vaccines with more components and a change in the vaccination schedule (starting at two instead of three months of age) may have contributed.

7.2.6 *International developments*

No relevant international developments to report.

7.2.7 *Literature*

1.* Schouls L, Schot C, De Voer RM, Van der Klis F, Knol M, Tcherniaeva I, et al. Lagging Immune Response to Haemophilus influenzae Serotype b (Hib) Conjugate Vaccine after the Primary Vaccination with Hib of Infants in The Netherlands. Vaccines. 2020;8(347).

*RIVM publication

7.3 Hepatitis B

I.K. Veldhuijzen, M. Visser, F. van Heiningen, B.H.B. van Benthem, J. Cremer, K.S.M. Benschop, A.J. King, H.E. de Melker

7.3.1 *Key points*

- Of the total number of 1205 reported hepatitis B cases, 9% have an acute infection and 91% a chronic infection.
- The incidence of acute hepatitis B notifications remained stable in 2019 at 0.6 per 100,000 population.
- Among both men and women, sexual contact was the most frequently reported risk factor for acute HBV infection.
- In 2019, genotype A continued to be the dominant genotype among acute HBV cases with 58% of 67 genotyped cases, followed by genotype F (18%).
- The number of newly diagnosed chronic HBV infections was 1,079, corresponding to an incidence of 6.2 per 100,000 population.

7.3.2 *Tables and figures*

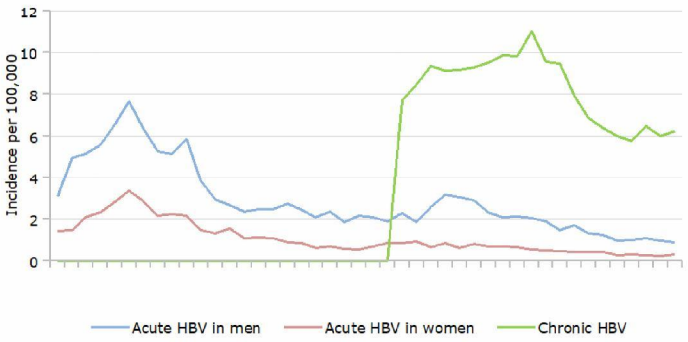


Figure 7.3.1 Incidence of acute HBV infections in men and women in the Netherlands from 1976 and chronic HBV infections from 2000
Source: Osiris

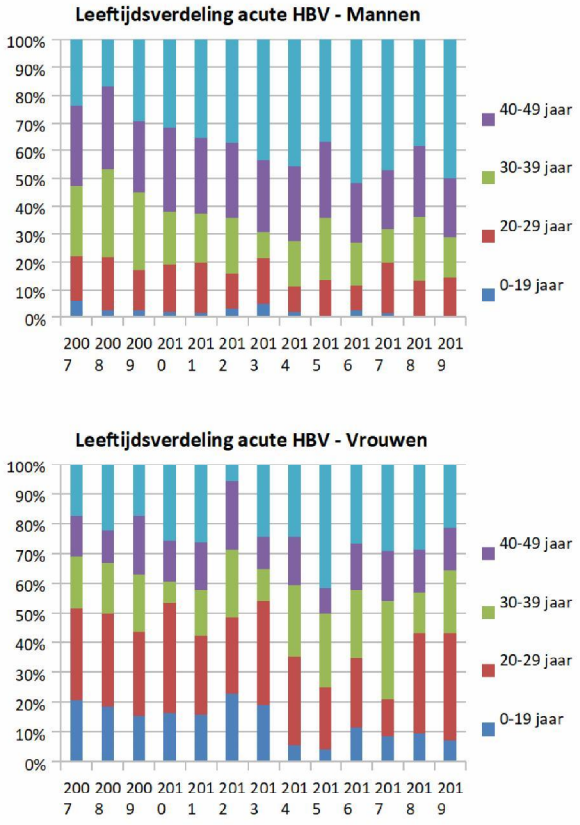


Figure 7.3.2 Age distribution of acute HBV infections in men and women in the Netherlands from 2007 to 2019

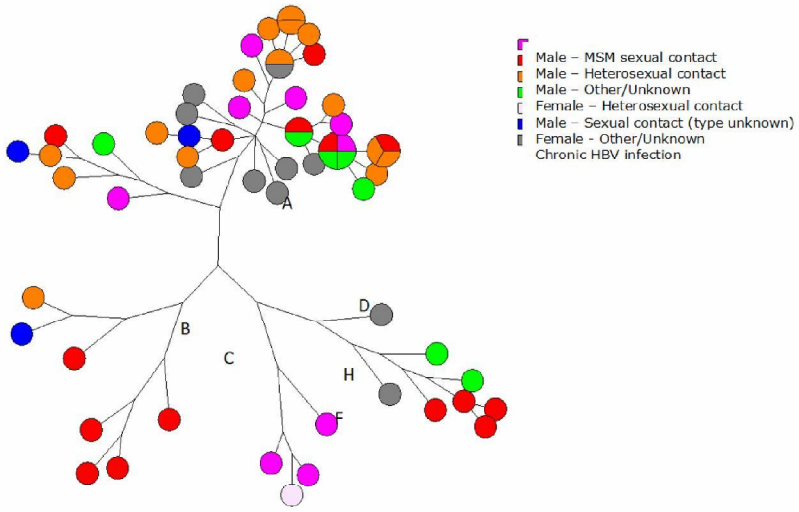
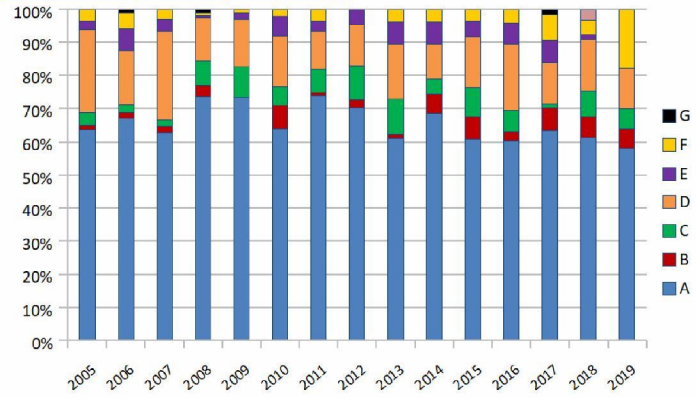


Figure 7.3.2 Optimised maximum parsimony tree based on the full length sequence of HBV cases in the Netherlands in 2018 by reported transmission route (n=60). gX: genotype

Alternatieve figuur over genotypering:



7.3.3 *Epidemiology*

In 2019, 1205 cases of hepatitis B virus (HBV) infection were notified. Of these, 1079 (91%) were chronic infections and 104 (9%) acute infections (22 cases unknown status).

7.3.3.1 Acute HBV epidemiology

The number of notified acute HBV infections was similar in 2019 compared to 2018. In the first half of 2020, 38 cases of acute HBV were reported. The incidence of acute HBV notifications in 2019 was 0.6 per 100,000 population, 0.9/100,000 among men and 0.3/100,000 among women. The HBV incidence seems to have stabilised since 2015 after having declined for both men and women since 2004 (Figure 7.3.1). The mean age of patients with acute HBV infection was 44.5 years and is higher in men (48.0) than in women (35.0). The age distribution of acute HBV infection by gender over time is shown in Figure 7.3.2. No cases of acute hepatitis B were reported among children; the youngest patient was 18 years old.

In the period September 2019 to January 2020 three patients died after a fulminant acute HBV infection. Since no mortality due to acute HBV infection was reported in the period 2013-2018 these three cases in a relatively short period are unusual. There was no indication of a common source as the patients were not epidemiologically or phylogenetically linked.

In 2019, most cases of acute HBV infection (58%) were acquired through sexual contact. For 33% of the reports of acute HBV infection, the most likely route of transmission remained unknown, despite source tracing. The proportion with unknown transmission route is higher for men (38%) than women (18%). Among men (76 cases), sexual contacts between MSM accounted for 20% of acute infections, and heterosexual transmission for 26%. Among women (28 cases), heterosexual contact accounted for 75% of cases. The majority of patients with acute hepatitis B were born in the Netherlands (75%).

7.3.3.2 Chronic HBV epidemiology

The number of chronic HBV notifications is around 1,000-1,100 per year since 2014 (incidence 5.8-6.4 per 100,000) (Figure 7.3.2). Since chronic hepatitis B is largely asymptomatic, the number of new diagnoses is highly influenced by testing practices. The number of people tested for HBV infection annually remains unknown.

In 2019, 89% of the chronic HBV patients where the country of birth was known were born abroad. The number of newly diagnosed chronic HBV infections in people born abroad is about 60 times higher than that of people born in the Netherlands (43 compared to 0.8 per 100,000 population. The number of notifications per country of birth fluctuates over time. In 2019 the most frequently reported countries of birth were China (n=99, 11%), Turkey (n=93, 10%) and Poland (n=48, 5%). Around 40 cases each where born in Eritrea, Ghana, Nigeria and Syria. Half of the cases acquired chronic HBV infection through vertical transmission. In around one third (37%) of reports of chronic HBV infection, the most likely route of transmission was unknown. Sexual contact was the source of infection of 4%, and for the remaining 9%, transmission may have occurred via other routes such as nosocomial transmission, needle stick injuries, or via injecting drug use (IDU).

In 2019, one case of perinatally acquired chronic HBV infection was diagnosed in a child born in the Netherlands in 2017. The child had

received more than three doses of vaccine but it was not reported whether immunoglobulin had been given at birth.

7.3.4 *Pathogen*

Samples for genotyping are collected from all acute HBV infections and from chronic infections in MSM and in people detected through the vaccination programme for behavioural risk groups. In 2019, samples were available for molecular typing of 74 acute HBV cases (71%) and 23 chronic HBV cases (2%). PCR amplification and sequencing gave results for 66(?) samples of HBV infections for the full length genome. An optimised maximum parsimony tree of these sequences by the most likely transmission route is shown in Figure 7.3.3. In 2019, 6 different genotypes were found (Genotype A-F). The largest cluster of cases continues to be among genotype A cases, the most common genotype for acute HBV in the Netherlands. Of acute cases with genotype information, 58% were genotype A. Genotype D used to be the second most detected genotype among acute cases, but in 2019 genotype F was more frequent (n=12, 18%) than genotype D (n=8, 12%). Genotype A was also most common among chronic cases in risk groups (9/22; 41%), followed by genotype D and E (both 3/22; 14%).

7.3.5 *Research*

7.3.5.1 Hepatitis B revaccination of non-responders

In a Dutch trial almost 500 healthy adults that were non-responders after a primary series of either HBVaxPro-10 or Engerix-B 20, were randomised to receive a second series of three doses of the same vaccine as control, or of Twinrix 20, Fendrix 20, or HBVaxPro 40. Three months after revaccination 67% of the control group had responded, compared to 80% in the Twinrix group, 83% in the HBVaxPro group and 97% in the Fendrix group. As the percentage responders compared to the control group was superior for the last two vaccines it was concluded that the indication for Fendrix and HBVaxPro-40 should be expanded to enable revaccination of non-responders [1].

7.3.6 *Literature*

1.* Raven SFH, 5.1.2e, Vossen 5.1.2e LG, Hautvast JLA, Roukens AHE, et al. Serological response to three alternative series of hepatitis B revaccination (Fendrix, Twinrix, and HBVaxPro-40) in healthy non-responders: a multicentre, open-label, randomised, controlled, superiority trial. Lancet Infect Dis. 2020;20(1):92-101.

* RIVM publication

7.4 Human papillomavirus (HPV)

J. Hoes, 5.1.2e. 5.1.2e 't Klooster, A.J. King, K. van Eer, H. Pasmans, B.H.B. van Benthem, A.W.M. Suijkerbuijk, J.A. Bogaards, F.R.M. van der Klis, H.E. de Melker

7.4.1 *Key points*

- High vaccine effectiveness (VE) against vaccine types HPV16/18 was found for persistent cervicovaginal infections up to nine years post-vaccination.
- Following vaccination with a two-dose schedule high seroprevalence and antibody levels against vaccine-types HPV16/18 up to 72 months of follow-up.
- Vaccinated women 12-24 years of age had a lower risk for a positive hrHPV test in the cervical smear, ASC-US or worse and (H)SIL or worse than unvaccinated women of the same age.
- Bivalent HPV vaccination provides partial protection against GW, especially when administered in early adolescence.

7.4.2 *Tables and figures*

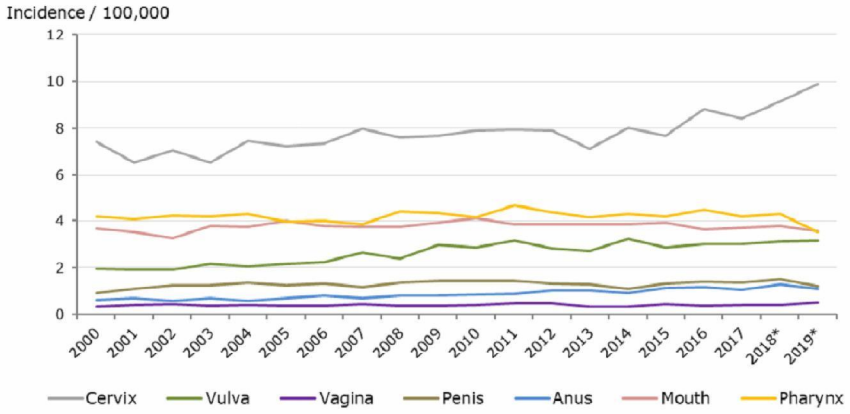


Figure 7.4.1 Incidence / 100,000 (standardised by the European standardised rate) of new cervical, anogenital, mouth/oral and pharynx/pharyngeal cancer cases in the Netherlands in the 2000-2019 period, by cancer type
* Preliminary figures
Source: the Netherlands Cancer Registry (NKR)

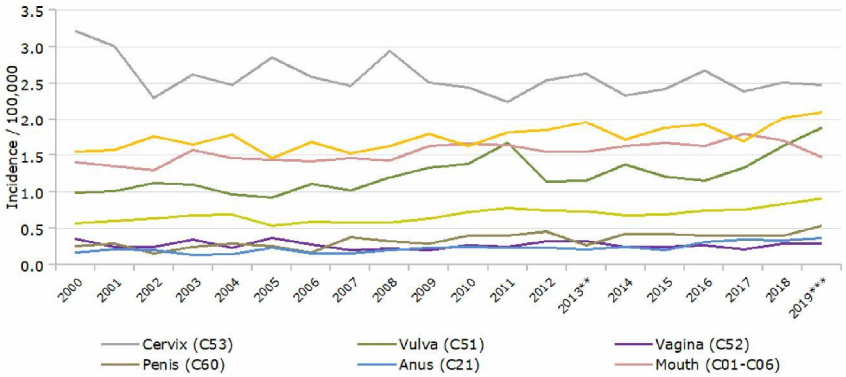


Figure 7.4.2 Incidence / 100,000 of deaths related to cervical, anogenital, mouth, oropharynx and pharynx cancer cases in the Netherlands in the 2000-2019 period, by cancer type

* Number of deaths due to pharynx cancer includes the number of oropharynx cancer deaths.

** In 2013, CBS started to use international software for automatically coding the causes of death. This makes the number more reproducible and internationally comparable. Due to this change, there have been some significant shifts seen in the causes of death.

*** Preliminary figures

Source: CBS

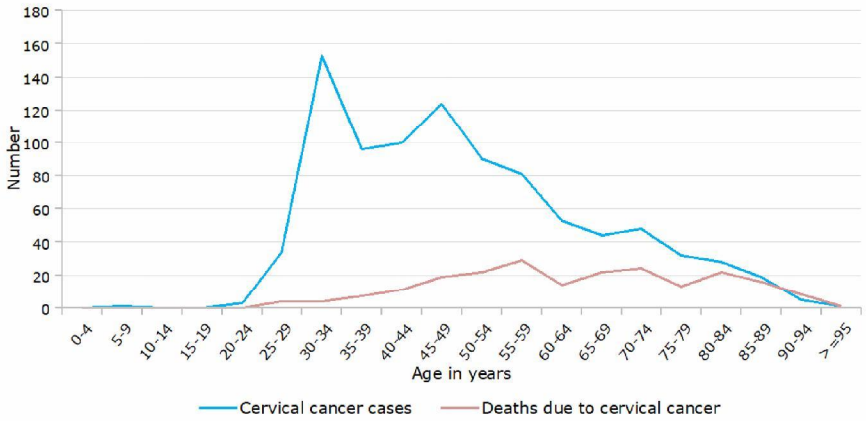


*Figure 7.4.3 Age-specific number of cervical cancer cases and deaths due to cervical cancer in the Netherlands in 2019**

* Preliminary data

Table 7.4.1 Vaccine effectiveness against incident and persistent HPV infections in young women in the HAVANA study up to nine years post vaccination

Incident infections	Adjusted *VE (95% CI)
Vaccine types (HPV16/18)	78.5% (68.4-85.4%)
Cross protective types (HPV31/45)	62.6% (45.5-74.4%)
Cross protective types (HPV31/33/45)	49.9% (32.1-63.0%)
Vaccine and cross protectives types (HPV16/18/31/45)	68.2% (58.3-75.8%)
hrHPV types	14.3% (3.1-24.1%)
Types 9valent vaccine (HPV6/11/16/18/31/33/45/52/58)	32.6% (21.3-42.2%)
Persistent infections (12 months)	**Adjusted* VE (95% CI)**
Vaccine types (HPV16/18)	95.8% (86.6-98.7%)
Cross protective types (HPV31/45)	82.6% (60.8-92.3%)
Cross protective types (HPV31/33/45)	65.0% (38.5-80.1%)
Vaccine and cross protectives types (HPV16/18/31/45)	89.6% (79.8-94.6%)
hrHPV types	22.4% (6.0-35.9%)
Types 9valent vaccine (HPV6/11/16/18/31/33/45/52/58)	49.3% (34.0-61.1%)

*Adjusted for age, urbanization degree, ever smoked, ever had sexual intercourse, ever used contraception.

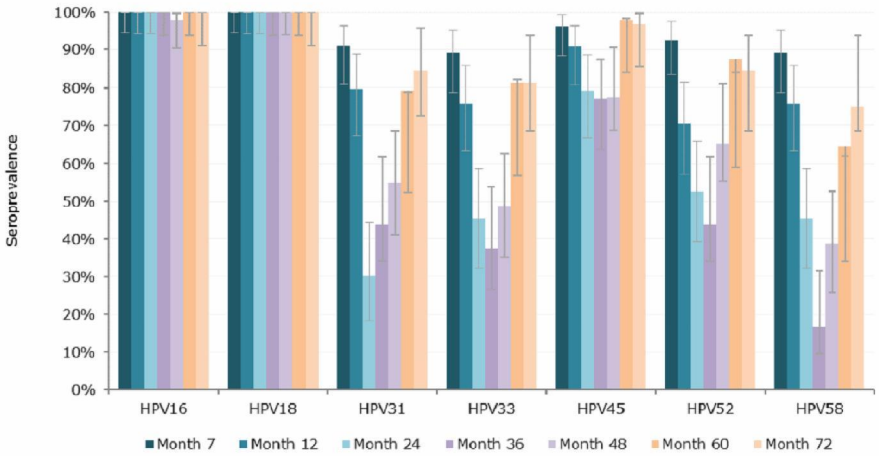


Figure 7.4.4. Seroprevalence among HPV2D participants of HPV types 16/18/31/33/45/52/58 following a two-dose schedule (0, 6 months) at 7, 12, 24, 36, 48, 60 and 72 months after the first dose

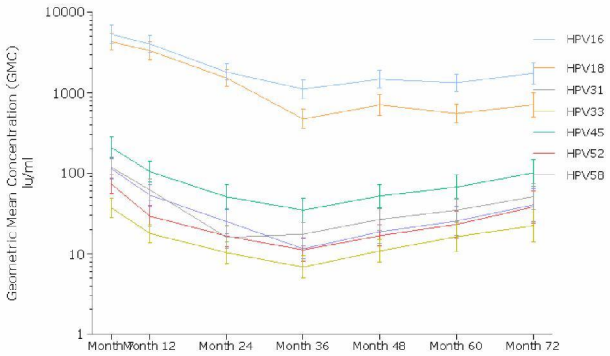


Figure 7.4.5. Geometric Mean Concentrations (GMC; lu/ml) among HPV2D participants of HPV types 16/18/31/33/45/52/58 following a two-dose schedule (0, 6 months) at 7, 12, 24, 36, 48, 60 and 72 months after the first dose

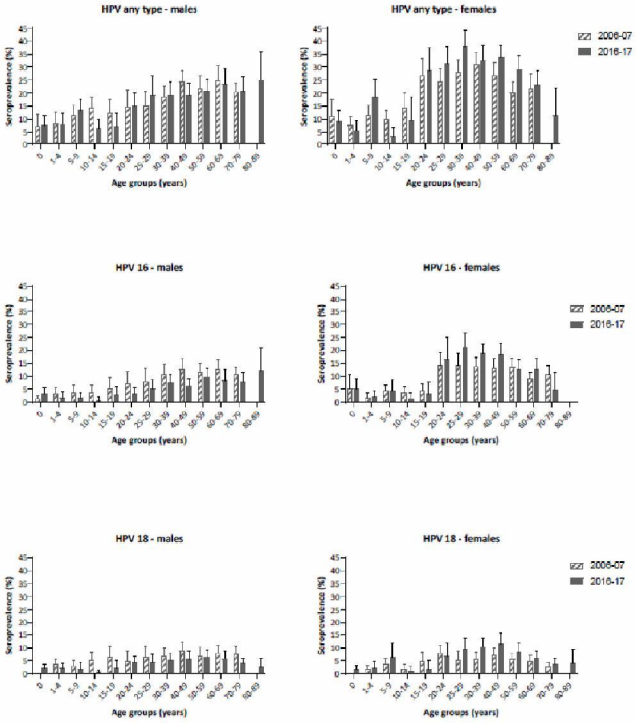


Figure 7.4.6 Seroprevalence of any HPV type (including HPV16/18/31/33/45/52/58), HPV16, and HPV18 in Pienter2 (2006-2007) and Pienter3 (2016-2017) stratified for gender and age group

Table 7.4.2 Association between bivalent HPV vaccination and AGW diagnosed by GPs

Vaccination status	N[a]	Observation time in years	AGW diagnoses	aIRR[b] (95%CI)	aIRR[c] (95%CI)
Unvaccinated	66,487	144,129	296	Reference	Reference
Vaccinated (≥1 dose)	58,299	180,497	310	0.76 (0.65 - 0.89)	0.75 (0.64 - 0.88)
Unvaccinated	66,487	144,129	296	Reference	Reference
Partially vaccinated[d]	31,790	26,409	42	1.15 (0.82 - 1.57)	0.96 (0.68 - 1.32)
Fully vaccinated[d]	53,389	154,088	268	0.72 (0.61 - 0.85)	0.72 (0.61 - 0.86)

Abbreviations: 95%CI: 95% confidence interval; AGW: anogenital warts; aIRR: adjusted incidence rate ratio; GP: general practitioner.
a Number of women that contributed observation time per vaccination status. One woman could contribute observation time to more than one vaccination status. Women with missing educational level were excluded.
b Adjusted for age as time-varying.
c Adjusted for age as time-varying, migration background, educational level, fear of STI/HIV consultations, mean number of GP consultations per years.
d Partially vaccinated: 1 dose or 2 doses <5 months apart. Fully vaccinated: 3 doses or 2 doses ≥5 months apart.

7.4.3 Epidemiology

Human papillomaviruses (HPVs) are a group of DNA viruses infecting cutaneous and mucosal epithelia throughout the human body. Over 200 different HPV types based on DNA sequencing have been identified to date, which differ from each other by at least 10% in the highly conserved L1 gene sequence. A persistent infection with a high-risk HPV (hrHPV) type can lead to the development of (pre-)cancerous lesions at different anogenital and oropharyngeal sites. Thirteen types of HPV are currently considered to be hrHPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). Virtually all cervical cancers are caused by HPV infections. Globally, this led to an estimated 311,000 deaths in 2018, mostly affecting middle-aged women [1]. HPV can also cause vaginal, vulvar, penile, anal, mouth/oral and oropharyngeal cancer. The

relative contribution of hrHPV16 and HPV18 is around 70% to all HPV

-attributable cancers, making them important vaccine targets.

The incidence of cervical cancer in the Netherlands is increasing over the last years to 9.90 per 100,000 in 2019 (preliminary data) (Figure 7.4.1). The number of deaths due to cervical cancer remained relatively stable in 2019 with 2.48 deaths per 100,000 (preliminary data), compared with 2.51 per 100,000 in 2018 (Figure 7.4.2). Incidences and deaths related to other HPV-associated cancers in the Netherlands have remained stable over the last five years (Figure 7.4.1 and Figure 7.4.2). Annually in the Netherlands, approximately 600-850 women are diagnosed with cervical cancer and around 200 women die due to the disease. The age-specific number of cervical cancer cases and deaths caused by cervical cancer in the Netherlands is shown in Figure 7.4.3.

The non-oncogenic, low-risk HPV (lrHPV) types 6 and 11 can cause genital warts (GW). In 2019, the number of GW diagnoses at sexual health centres (SHC) was 928 [2]. The number of diagnoses of GW by GPs was estimated at 44,700 in 2018, which was comparable to figures for the past three years.

7.4.4 Current/ongoing research

7.4.4.1 Whole genome sequencing analysis of HPV16 and HPV18

Whole genome sequence studies on HPV16 and HPV18 positive genital swabs taken from unvaccinated young women in the Netherlands revealed a high degree of host-unique HPV16/18 variants. Conversely, women with a persistent HPV16/18 infection maintained strong conservation of the consensus variant sequence [3, 4]. In vaccinated women, HPV16/18 DNA is also detected sporadically albeit in very low amounts (i.e. the viral load is generally low). Low HPV16/18 viral loads in vaccinated women pose a challenge for whole genome sequencing. To date primarily partial sequences of HPV16/18 genomes (NCR region and E6) isolated from vaccinated women are available. Based on these preliminary results HPV16/18 detected in vaccinated women do not cluster differently from HPV16/18 found in non-vaccinated women. With the improvement of sample processing techniques and deep sequencing, generating whole genome HPV sequences from vaccinated individuals will hopefully be successful in the (near) future.

7.4.4.2 HPV amongst vaccinated and unvaccinated adolescents (HAVANA)

A prospective cohort study (HAVANA) which was initiated in 2009 among vaccinated and unvaccinated 14- to 16-year-old girls, eligible for the catch-up campaign, is still ongoing. The primary aim of this study is to monitor the effect of the bivalent HPV vaccination on HPV-type specific presence amongst three-times vaccinated and unvaccinated young women. Vaginal self-swabs collected in this cohort were tested for the presence of HPV DNA. Vaccine effectiveness (VE) against incident and persistent infections is determined every year. The bivalent vaccine showed a significantly high VE against both incident and 12-month persisting vaccine type infections (HPV16/18) up to nine years post-vaccination. High VE against cross protective types was observed (HPV31/45) as well. Pooled VE estimates up to nine years post-vaccination against incident and persistent infections are shown in Table 7.4.1. Type-specific statistically significant VE up to nine years post-vaccination against 12-month persistent infection was found for: HPV16 (94.4%, 95%CI 81.8-98.3%); HPV18 (100%, model did not converge due to absence of infections among vaccinated); HPV31 (85.3%, 95%CI 62.0-94.3%); HPV45 (80.4%, 95%CI 7.5-95.8%). Statistically significant VE estimates against incident infections were found for the same HPV types and HPV35.

In 2016, a second prospective cohort study (HAVANA2) was started among vaccinated and unvaccinated girls (birth cohort 2001). These girls were the first who were eligible for the two-dose HPV vaccination schedule, which initiated in 2014. Follow-up of this cohort is done yearly for at least five years in which girls are asked to fill out a questionnaire

and hand in a vaginal self-swab. For the first round of this study, 39,261 girls were invited for participation. After three years of follow-up (FU), data of 2476 girls could be used of whom 53.1% was vaccinated. Although the absolute number of HPV infections was still low, preliminary vaccine effectiveness against incident infections could be estimated. This resulted in a VE of 82.6% (95% CI 19.9-96.2%) against incident HPV16/18 infections and of 82.4% (95% CI 18.1-96.2%) against HPV31/45 infections. This indicates that the two-dose schedule provides high protection in a population-setting against both vaccine and cross protective HPV types up to four years post-vaccination.

7.4.4.3 Performance of HPV detection of HPV type 59 and HPV type 45 with the SPF10 system

The broad spectrum L1-based SPF10-DEIA LIPA25 system is widely used for HPV detection and typing in many epidemiological studies including the studies performed by the RIVM. This assay is known to be highly sensitive for most high-risk HPVs but is less sensitive at detecting HPV45 and HPV59 infections. We investigated the HPV45 and HPV59 detection sensitivity of the SPF10 system and compared it to detection with type specific HPV45- and HPV59 qPCR assays. Missed HPV45 and HPV59 infections had significant lower viral loads compared to detected HPV45 and HPV59. Preliminary data suggest that HPV59 infections in non-vaccinated participants were missed more frequently with the SPF10 detection system. Interestingly, HPV59 detection seemed more hampered by the presence of co-occurring HPV types compared to HPV45. SPF10 detection of HPV59 was likely most hampered in non-vaccinated individuals, as they often carry more HPV types. As a result, a great impact on vaccine effectivity (VE) estimates for HPV59 was observed based on the SPF10 method (strong negative) and the TS qPCR assay (no apparent VE effect), while this change was not observed for HPV45.

7.4.4.4 Monitoring the immunogenicity of the two-dose schedule (HPV-2D)

To monitor the quality and quantity of the generated immune response following a two-dose vaccination schedule, a cohort study among the first birth cohort that was eligible for vaccination with a two-dose schedule, i.e. birth cohort 2001, started in 2014. Annually, girls donate a blood sample and fill in questionnaire. To date results were available up to the sixth year. These results showed high seroprevalence and antibody levels against vaccine-types HPV16/18 up to 72 months of follow-up (Figure 7.4.4 and Figure 7.4.5). Waning in antibody levels was seen up to 36 months, thereafter the levels remained stable (Figure 7.4.5). Seroprevalence and antibody levels were considerably lower for HPV types 31, 33, 45, 52, 58 (Figure 7.4.4 and Figure 7.4.5).

7.4.4.5 HPV (sero)prevalence among young MSM visiting the STI clinic (PASSYON study)

The PASSYON study is a biennial cross-sectional survey conducted among 16- to 24-year-old visitors of sexual health centers in the Netherlands [5]. We used data from MSM included in PASSYON study years 2009-2017. MSM provided a penile and anal swab for HPV DNA testing and blood for HPV antibody testing. There were no significant declines in the HPV prevalence among MSM up to eight years after introduction of girls-only HPV16/18 vaccination, indicating that MSM are

unlikely to benefit largely from herd effects from girls-only vaccination. Most MSM were vaccine-type DNA negative and seronegative, suggesting that vaccination of young MSM visiting SHCs could still be beneficial [6].

7.4.4.6 Trends in HPV16/18 positivity among female and heterosexual male STI clinic visitors (PASSYON study)

Using data from the PASSYON study from 2009-2017, we studied trends in the prevalence of 25 HPV types (including vaccine types) following the introduction of HPV vaccination in the Netherlands in 2009. Among all women, heterosexual men, and unvaccinated women a yearly percentual decline was observed for HPV16/18 ranging from 13% for all women and heterosexual men, to 5.4% for unvaccinated women. Additionally, we observed significant declines in HPV31 (all women and heterosexual men), HPV45 (all women), and in all high-risk HPV types pooled (all women and heterosexual men). Significant increases were observed for HPV56 (all women) and HPV52 (unvaccinated women). These results indicate both first and second order herd effects against vaccine types from girls-only vaccination up to 8 years post vaccination implementation. Moreover, heterosexual men also benefit from herd effects against cross protective types. These results are promising regarding population-level and clinical impact of girls-only HPV16/18 vaccination in a country with moderate vaccine uptake.

7.4.4.7 Genital warts in GP sentinel surveillance (NIVEL)

There is ongoing debate about the possible protective effect of the bivalent human papillomavirus (2vHPV) vaccine, targeting oncogenic types HPV16/18, against anogenital warts (AGW), commonly attributed to HPV6/11. We performed a retrospective registry-based open cohort study to assess the effect of 2vHPV vaccination on AGW. We linked general practitioners (GPs) data from women born between 1993-2002, who had been eligible for HPV vaccination in the Netherlands, to the Dutch national immunization registry on an individual level. Women were followed until their first AGW diagnosis or end of follow-up. We linked data of 96,468 women with in total 328,019 years observation time and 613 AGW diagnoses (incidence: 1.87/1,000 person-years). The AGW incidence was lower among those with ≥1 dose versus 0 doses (adjusted incidence rate ratio 0.75, 95% confidence interval (CI) 0.64-0.88) (Table 7.4.2). This is the largest population-based study so far to examine the effect of 2vHPV vaccination on AGW, with reliable individual information on AGW diagnoses and vaccination status. The results indicate that 2vHPV vaccination partially protects against AGW, especially when administered in early adolescence [7].

7.4.4.8 Trend analysis of cytological abnormalities in opportunistic cervical screening among young women in the Netherlands

HPV-vaccine eligible girls will enter the Dutch cervical screening program at 30 years of age, i.e. from 2023 onwards. However, it appears that every year a substantial number of young women before the age of 30 have a cervical smear test taken outside the regular screening program. In this study we used data of opportunistic screening to explore trends in cytological abnormalities and to indicate possible early effects of HPV vaccination. Therefore, women with a cervical smear test before than 30 years of age between 1995 and 2016 from the nationwide network and

registry of histo- and cytopathology in the Netherlands (PALGA) were analyzed. Annually, on average 42,500 (range 29,419 to 105,812) girls younger than 30 years of age (0.025% of the population) had a cervical smear test taken between 2000 and 2016. The percentage of atypical squamous cells of undetermined significance (ASC-US) is increasing since 2001. The percentage also increases with age up to the age of 24 and thereafter declines again. The percentage of high-grade squamous intraepithelial lesions ((H)SIL) remained stable up to 2006 but increased thereafter. The percentage of (H)SIL increases steadily with age. The increasing trend has not been halted by HPV vaccination yet, which is likely due to the rather young age of vaccine-eligible girls in the study period (i.e. up to 23 years of age) and the suboptimal vaccination coverage in the Netherlands (46-61%).

7.4.4.9 Effect of HPV vaccination on cervical lesions in opportunistic screening among young women in the Netherlands

In 2023 the first girls who were eligible for HPV-vaccination, will enter the cervical screening program. However, a substantial number of young women have a cervical smear test taken before the start of the regular screening program. This study was initiated to explore possible early effects of HPV-vaccination on cervical lesions in opportunistic screening. In this study, cytology results of cervical smear tests from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) were linked to the women's HPV-vaccination status from the national vaccination registry (Praeventis). The cohort consists of girls eligible for HPV-vaccination (i.e. born from 1993 onwards) who have had a cervical smear test taken between 2009 and March 2018. A total of 42,214 young women did have one or more cervical smear tests during the study period. Percentages of vaccination coverage among these young women were comparable with the national vaccination coverage (45-61%). Results of logistic regression analysis showed that fully vaccinated women 12-24 years of age had a lower risk for hrHPV (OR corrected for age and birth cohort: 0.68; 95%CI 0.62-0.74), ASC-US or worse (OR: 0.77; 95%CI 0.73-0.82) and (H)SIL or worse (OR: 0.45; 0.37-0.56) than unvaccinated women of the same age. In incompletely vaccinated girls a smaller effect was seen than in fully vaccinated girls, i.e. for hrHPV 0.75 (0.61-0.93) for ASC-US or worse 0.96 (0.86-1.08) and for (H)SIL or worse 0.60 (0.38-0.96). So, by linking nation-wide registries on cytopathology and vaccination, we were able to show significant early effects of HPV-vaccination on cervical lesions in young women even before the start of the cervical screening program.

7.4.4.10 Determinants of HPV-vaccination uptake over time in the Netherlands

This study was initiated to gain insight into the relationship between social, economic, cultural and political factors and the vaccination rate and whether the influence of these factors changed over time. Results showed that having not received a MMR-vaccination, having one or two parents born in Morocco, Turkey or two parents born in the Netherlands Antilles and Aruba, a lower socioeconomic status, higher urbanization level, higher road distance and higher voting proportions in municipalities for Christian political parties and populist parties with liberal-conservative views were associated with a lower HPV-vaccination uptake. Besides some changes in political preferences of the population

we found no clear determinants which could possibly explain the decrease in the HPV-vaccination uptake.

7.4.4.11 HPV seroprevalence in the Netherlands (Pienter studies)

As the bivalent HPV-vaccination was included in the National Immunization Program in the Netherlands, we examined the possible changes in HPV-seroprevalence in the HPV unvaccinated Dutch population aged 0-89 years by comparing pre-vaccination data with data of approximately six years post-implementation of national vaccination. We therefore made use of the Pienter studies, were we collected serum samples of men and women, performed before (2006-07, n=6384) and after (2016-17, n=5645) implementation of HPV-vaccination in the Netherlands. Seven high-risk HPV-specific antibodies (HPV16, 18, 31, 33, 45, 52, and 58) were tested in a virus-like-particle-based multiplex-immunoassay. Type-specific HPV-seroprevalence had increased in women between 2006-07 and 2016-17. Also, a higher seroprevalence for at least one type in women >15 years was found in 2016-17 (31.7%) compared with 2006-07 (25.2%). In men, overall HPV seroprevalence remained similar, however a lower seroprevalence was found for HPV16 in 2016-17 (7.5%) compared with 2006-07 (10.6%). These results indicate an increase in exposure of high-risk HPV types in women and a rather stable exposure in men. No clear effects of the strategy of girls-only vaccination were observed in men, probably because of the short time after introduction combined with suboptimal vaccination coverage.

7.4.4.12 HPV seroprevalence on the BES-islands

Incidence and mortality of human papillomavirus (HPV)-related cancers differs geographically, with high rates in Caribbean countries. Seroepidemiological data could therefore provide information on lifetime cumulative HPV exposure and contributing risk factors, but this has not been available yet for Caribbean Netherlands (CN), comprising the islands Bonaire, St. Eustatius and Saba. Therefore, a cross-sectional population-based serosurveillance study was performed in this (recently girls-only HPV-vaccinated) population in 2017. Blood samples from participants (n=1,823, 0-90 years) were tested for seven high-risk (hr)-HPV-specific IgG-antibodies using a VLP-based multiplex-immunoassay. We found that among individuals aged ≥15 years, overall seropositivity was high (34.0%), with over half of them being seropositive for ≥2 hr-HPV types, and HPV16 and 52 being most prevalent (13%). Seroprevalence was substantial higher in women (51%) than men (18%), predominantly peaking in women aged 20-59 years, and was highest on St. Eustatius (38%). In accordance with the Caribbean region, seroprevalence of multiple hr-HPV types was high in CN. These data corroborate the decision regarding introduction of a sex-neutral HPV-vaccination program and the relevance for considering a population-based cervical cancer screening program [8].

7.4.4.13 Modelling

In May 2018, the Director-General of the WHO made a global call for action aiming to eliminate cervical cancer. This initiative is currently

investigating which approaches can accomplish this mission within the 21st century. Two recent studies assessing the health impact of girls' HPV vaccination strategies, found that it would require at least 90% uptake in girls to achieve the WHO target levels for the near-elimination of cervical cancer incidence and mortality in many low- and middle-income countries [9, 10]. Previous modelling studies have suggested that the same holds for high-income countries. However, such consistent high coverage is hard to achieve and elimination of oncogenic HPV types might already be achieved with moderate vaccination coverage if a sex-neutral strategy is applied [11]. Moreover, the population impact will depend on the HPV vaccine type and the specific vaccination strategy in place [12], as well as on the still unresolved possibility of type replacement [13].

A recent modelling study, based on a Finnish community-randomized trial comparing sex-neutral as well as girls-only HPV16/18 vaccination to a control (hepatitis B-virus vaccination) arm, predicted that 75% coverage in a sex-neutral program could suffice to eliminate vaccine types HPV16/18 as well as cross-protective types HPV31/33 [14]. Therefore, the authors claim that sex-neutral vaccination is "superior for eradication of oncogenic HPVs" [14]. Note, however, that 75% coverage in both sexes constitutes a higher absolute vaccine administration than full coverage in a single-sex program [11].

7.4.5 International developments

Following the call from the WHO Director General in 2018, a Draft Strategy for the elimination of cervical cancer as a public health problem was put for the World Health Assembly's approval in May 2020 [15]. The Draft Global Strategy outlines that cervical cancer is eliminated as a public health problem when all countries reach an incidence rate of less than 4 cases per 100,000 women. To reach elimination, efforts must be aligned and accelerated. Every country must reach the following global targets by 2030:

- 90% coverage of HPV vaccination of girls (by 15 years of age);
- 70% coverage of screening (70% of women are screened with high-performance tests by the ages of 35 and 45 years) and 90% treatment of precancerous lesions;
- Management of 90% of invasive cancer cases.

7.4.5.1 Impact of HPV vaccination

In a community-randomized trial from Finland, vaccine effectiveness of the HPV16/18 vaccine against oropharyngeal HPV infections could be determined. This study showed VE estimates up to 6 years post-vaccination among females aged 18,5 years. Highest effectiveness was observed against HPV16/18 infections, (82.4% (95% confidence intervals [CI]: 47.3–94.1), while VE was 69.9% (95% CI: 29.6–87.1) for HPV 31/33/45 infections. This indicates the AS04-HPV-16/18 vaccine is effective against oropharyngeal HPV infections and could aid in the reduction of head- and neck-cancers [16].

The incidence of vulvar pre-cancer and cancer was examined in Denmark over the 1997–2018 period. Age-standardized and age specific incidence rates of vulvar squamous cell carcinoma (VSCC) and precancerous lesions were expressed using the average annual percentage change (AAPC). The age-standardized incidence rate of VSCC showed an average yearly increase of 2.95% (95%CI: 2.15–3.75) in the study period, like the incidence of vulvar precancerous lesions (AAPC = 2.38%; 95%CI: 1.75–3.02). After implementation of HPV vaccination, the incidence of vulvar precancerous lesions decreased significantly in women aged <20 years (AAPC =−22.10% (95%CI: −35.27 to −6.26)) and 20–29 years (AAPC=−6.57, 95% CI: −10.63 to −2.33), whereas the incidence increased in most age groups ≥50 years. This indicates that, although overall incidence of vulvar (pre-) cancer was increasing, a possible positive effect of HPV vaccination was observed in vaccine-eligible age groups [17].

In order to obtain insight into the range of the cross-protective effect of the bivalent HPV vaccine, pooled efficacy estimates based on individual-level data from two randomized controlled trials were established against incident HPV infections and cervical abnormalities. Statistically significant efficacy was observed for individual oncogenic types 16/18/31/33/45/52 and nononcogenic types 6/11/53/74 6-month persisting infections. Efficacy against cervical abnormalities (caused by all HPV types) increased with severity, ranging from 27.7% (95% CI 21.7% to 33.3%) to 58.7% (95% CI 34.1% to 74.7%) for cytologic outcomes and 66.0% (95% CI 54.4% to 74.9%) to 87.8% (95% CI 71.1% to 95.7%) for histologic outcomes (CIN2+ and CIN3+, respectively). This indicates that bivalent HPV vaccination probably provides some additional cross protection besides established types, which could lead to higher efficacy against clinical outcomes [18].

A head-to-head comparison was made regarding GW incidence rates (IRs) in Norway and Denmark following quadrivalent HPV vaccination. Both countries started routine vaccination for 12-year-old girls in 2009, but Denmark additionally offered vaccination for older age groups. HPV vaccination coverage among women aged 12–35 years in 2015 was 24% in Norway and 70% in Denmark. GWs IRs in Norway and Denmark decreased annually in 2009–2015 among women by 4.8% (95% confidence interval: 4.3 to 5.3) and 18.0% (95%CI: 17.5 to 18.6), respectively, and among men by 1.9% (95%CI: 1.4 to 2.4) and 10.7% (95%CI: 10.3 to 11.2), respectively. This indicates that vaccination catch-up campaigns can aid in fast(er) declines of HPV related morbidity, both in women and in unvaccinated men. However, high vaccine uptake is important to accomplish this [19].

Potential human papillomavirus (HPV) vaccination and cervical screening scenarios in low-income and lower-middle-income countries (LMICs) were modelled to examine the feasibility and timing of elimination of cervical cancer. Three base-case scenarios were compared: girls-only vaccination, girls-only vaccination and once-lifetime screening, and girls-only vaccination and twice-lifetime screening. Different elimination thresholds were studied: an average age-standardized cervical cancer incidence of four or fewer cases per 100 000 women-years, ten or fewer

cases per 100 000 women-years, or an 85% or greater reduction in incidence. Girls-only HPV vaccination was predicted to reduce the median age-standardized cervical cancer incidence in LMICs from 19.8 (range 19.4–19.8) to 2.1 (2.0–2.6) cases per 100 000 women-years over the next century (89.4% [86.2–90.1] reduction). Adding twice-lifetime screening reduced the incidence to 0.7 (0.6–1.6) cases per 100 000 women-years (96.7% [91.3–96.7] reduction). Girls-only vaccination was predicted to result in elimination in 60% (58–65) of LMICs based on the threshold of four or fewer cases per 100 000 women-years, in 99% (89–100) of LMICs based on the threshold of ten or fewer cases per 100 000 women-years, and in 87% (37–99) of LMICs based on the 85% or greater reduction threshold. When adding twice-lifetime screening, 100% (71–100) of LMICs reached elimination for all three thresholds. This indicates that high HPV vaccination uptake can lead to the elimination of cervical cancer in most LMCI's. This is endorsed as an important public health goal by the WHO [9].

7.4.5.2 Reduced dosing schedule

A two-dose schedule is currently the most often used in national immunization programs worldwide. However, since a few years attention has arose for a one-dose HPV vaccine schedule. In several studies one dose recipients showed robust and sustained antibody levels against HPV16 and HPV18 over a nine-year period. Although being inferior to two- and three dose vaccinated girls, frequencies of incident and persistent HPV16 and HPV18 infections were similar and uniformly low in all the different doses groups up to 7 years of follow-up [20-22]. Moreover, cellular immunity followed a one-dose schedule was detectable after 6 years [23, 24].

These data suggest that either a single dose of the bivalent or quadrivalent HPV vaccine has comparable effectiveness and is immunogenic, which could give long-lasting protection against infections against HPV-vaccine types. Therefore, a one dose vaccination could be a viable strategy when working towards the global elimination of cervical cancer. Randomized controlled trials with a focus on evaluation on the protection afforded by a single dose of HPV vaccine are now on its way. Results are to be expected in the upcoming years.

7.4.5.3 Cost-effectiveness

Datta et al. assessed the cost-effectiveness of HPV vaccination for both girls and boys in the UK. In an economic model healthcare costs and quality-adjusted life years were assessed using the three HPV vaccines currently available, vaccinating either girls alone or both sexes. Vaccinating girls is extremely cost-effective compared with no vaccination, vaccinating both sexes is less so. Adding boys to an already successful girls-only programme has a low cost-effectiveness, as males have high protection through herd immunity. The generic conclusion from this work is that as coverage in girls increases, there is less incremental benefit from adding boys to the programme, due to existing herd immunity. In the case of the UK, with a high reported sustained HPV vaccine uptake rates in girls, it is unlikely that adding boys will be cost-effective within standard economic guidelines which assume a 3.5% economic discounting. However, given the long time-scales associated

with HPV infection and resulting disease, it may be more appropriate to adopt a 1.5% discounting, as is used in the Netherlands, in which case adding boys to the programme becomes cost-effective for all three vaccines considered [25].

In the United States, the routine age for HPV vaccination is 11 to 12 years, with catch-up vaccination through age 26 years for women and 21 years for men. U.S. vaccination policy on use of the 9-valent HPV vaccine in adult women and men is being reviewed. Laprise et al. evaluated the cost-effectiveness of extending the current U.S. The current HPV vaccination program is predicted to be cost saving. Vaccinating women and men up to age 30, 40, and 45 years is predicted to cost $830,000, $1,843,000, and $1,471,000, respectively, per quality-adjusted life-year gained (vs. current vaccination). To conclude, extending vaccination to older ages is predicted to produce small additional health benefits and result in substantially higher incremental cost-effectiveness ratios than the current recommendation [26].

Mahumud et al assessed the cost-effectiveness of adding a nonavalent new Gardasil-9® (9vHPV) vaccine to the national immunization schedule in Australia across three different delivery strategies [27]. The 9vHPV vaccination was estimated to prevent 113 new cases of cervical cancer (discounted) during a 20-year period compared with the quadrivalent 4vHPV vaccine. Considering delivery strategies, the ICERs per DALY averted were A$46,378, A$43,729, and A$43,930 for school, health facilities, and outreach-based vaccination programs from the societal perspective. All estimates of ICERs fell below the threshold level (A$73,267). This cost-effectiveness evaluation suggests that the routine two-dose 9vHPV vaccination strategy of preadolescent girls against HPV is very cost-effective in Australia.

7.4.5.4 Screening uptake

Chua et al. studied the influence of HPV vaccination on high-risk sexual behaviour, and intention for cervical screening among young Chinese females [28]. The study was conducted in secondary schools (in-school) and among community females between 18 and 27 years (out-school). They showed that vaccinated Chinese young females had a higher intention for cervical screening, i.e. 23.6% vs. 21.1% for in-school girls and 53.6% vs. 43.6% for out-school females. Costs and knowledge were important factors for non-vaccination and non-intention for cervical screening.

7.4.5.5 Male vaccination

In light of the global HPV vaccine supply shortage, the WHO Strategic Advisory Group of Experts (SAGE) proposed to temporarily pause implementation of male HPV vaccination programs [29]. The supply shortage is most likely only temporary and, as also mentioned in the 2019 SAGE meeting, it is to the responsibility of 'the vaccine manufacturers to be operationally and ethically responsive to global vaccine supply needs and align with WHO´s call for action for elimination of cervical cancer' [29]. Moreover, countries still need to weigh local vaccine coverage, disease burden, and considerations of (economic) efficiency in order to support local decision making.

To further the discussion on the economic efficiency of sex-neutral HPV vaccination in high-income settings, a systematic account of its incremental cost-effectiveness relative to girls-only vaccination is needed. The majority of studies that evaluated sex-neutral compared to girls-only HPV vaccination concluded that preadolescent male vaccination would not be cost-effective, primarily owing to assumptions of high vaccine uptake among girls and high costs of vaccination [30]. However, in most European countries, vaccine uptake among girls has been lower than anticipated [31], while strong vaccine price reductions have been realized via tendering procedures and adoption of reduced dosing schemes [32].

For this reason, we investigated the cost-effectiveness of sex-neutral HPV vaccination in European settings with information on tender-based vaccine prices, taking actual levels of vaccine coverage into account. A Bayesian synthesis framework for health economic evaluation was applied that accommodated country-specific information on key epidemiologic and economic parameters. To tailor region-specific herd effects, we used projections from three independently developed HPV transmission models. We found that sex-neutral HPV vaccination is economically attractive in all European tender-based settings. Still, tendering mechanisms need to ensure that boys' vaccination will remain cost-effective at high vaccine uptake rates, as sex-neutral vaccination remained cost-effective in 8 out of the 11 countries included at an assumed 80% uptake in both sexes [33].

7.4.6 Literature

7.4.6.1 References

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