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Germ factories or immune boot camps? Infection and immunity in childcare settings

Sarah L. Caddy,[1,2] Lucy van Dorp,[3] Leo Swadling,[4] Yuan Wis Wang-Koh,[5] Charlotte J. Houldcroft[6]

AUTHOR AFFILIATIONS See affiliation list on p. 22.

SUMMARY Childcare outside the home is a common experience for many children in high-income countries. It is associated with an increase in the incidence of infectious diseases—not just for the child but also for their parents and other household members. In this review, we explore this phenomenon from multiple angles, combining age at first infection, maternal antibody dynamics, seroepidemiology, cohort studies, and outbreak reports to understand the relationship between the immune systems of children starting childcare and the pathogen milieu they encounter. We consider the interaction between the age at which many infants begin out-of-home childcare and the maturation of cellular and humoral immunity. We bring together data on what is "normal" for infections in the first years of life: the range and incidence of gastrointestinal, respiratory, and rash-forming illnesses that typically infect young children. We review evidence of the additional impact that childcare has on the transmission of these pathogens. The economic and personal impacts of these illnesses are considered, including our lived experiences. We ask whether there are effective interventions to reduce illness associated with childcare, as the UK adds chickenpox to the childhood vaccination schedule. Finally, we consider evidence suggesting a trade-off between infections earlier in life and

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Peer Reviewer Alasdair Munro, NIHR Southampton Clinical Research Facility and Biomedical Research Centre, Southampton, United Kingdom

Address correspondence to Charlotte J. Houldcroft, ch504@cam.ac.uk.

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when children start formal schooling. We conclude that the high burden of infection in young children is normal, linked to the immunobiology of infants and the transmission dynamics of individual pathogens, but the collective impact of these infections is underappreciated.

KEYWORDS maternal antibodies, childcare settings, age at primary infection

INTRODUCTION

Childcare outside the home is a common, and increasingly predominant, experience for infants and children in the United Kingdom (UK) (1), the USA (2), Australia, and the European Union (3). This entrance into formal childcare typically coincides with the end of maternity or shared parental leave, between 6 and 12 months of age (albeit with regional variations). Anecdotally, it is well known among parents that when their children start to attend formal out-of-home childcare—be that a nursery/daycare/kindergarten setting or attending the home of a childminder—this is associated with a succession of infectious diseases and illnesses that may keep the child at home, and which may also be transmitted to siblings, parents, and other carers. Some infections may have exclusion periods, after symptoms have ceased, before the child can return to childcare, with the aim of reducing onward transmission. Infection transmission can be intense throughout the period before formal schooling begins for childcare attendees, albeit diminishing as children age, and has emotional and financial implications for families. Recurrent infection disrupts the settling process for infants into a new childcare setting, can lead to missed work for parents, puts economic and social strain on families, increases demand on healthcare services, and, in rare cases, has the risk of severe outcomes.

Due to updated studies of disease burden, potential impact on shingles (zoster), and cost-effectiveness modeling, the UK added vaccination against varicella-zoster virus (VZV), the causative agent of chickenpox (varicella) and shingles, to the standard childhood vaccination schedule in 2026 (4)—a welcome addition, although lagging behind the USA, Australia, Spain, and many other European countries (5). With this in mind, it is time to reflect on what can be done to prevent or ameliorate infections that spread in childcare settings, and what can be learned through the study of 'germ factories or immune bootcamps' in infancy. It is also worthwhile considering whether eliminating infectious disease transmission in childcare settings is a desirable goal from an immunological perspective, or a realistic goal, given the transmission dynamics of many common childhood pathogens.

The diseases we discuss in this review are not unique to the childcare environment; they are common diseases of early childhood. However, participating in out-of-home childcare creates opportunities for these pathogens to transmit, which are enhanced by the presence of cohorts of relatively immune-naive infants and children from multiple households.

In this review, we bring together evidence from immunology, infectious disease genomics, and epidemiology to understand why children first starting formal childcare outside their own homes are apparently so susceptible to a range of different common childhood infections. We then discuss the economic and personal impacts of taking time off work to care for infants with some of the most common childcare illnesses. Finally, we discuss possible future interventions that may reduce transmission and call for a better understanding of the normal range of sick days children first starting childcare will experience.

INFANT AND TODDLER IMMUNE RESPONSE: IMMUNE NAIVETY AND THE DEVELOPMENT OF ADAPTIVE IMMUNITY THROUGH ANTIGEN EXPOSURE

Infants enter the world with a relatively immature and antigen-naive immune system, shaped by limited *in utero* exposure and still-developing immune functions. However, their risk of infectious disease is significantly reduced by the presence of maternal

antibodies. Immunoglobulin G (IgG) made by the mother is transferred across the placenta to the infant's circulation during the third trimester of pregnancy, and immunoglobulin A (IgA) maternal antibodies are delivered via breast milk postnatally to provide mucosal protection (6, 7). Infants born with low levels of maternal antibodies (e.g., premature infants or those born to HIV-positive mothers) are expected to be at increased risk of infectious disease as neonates (8, 9).

Maternal IgG in the infant circulation wanes over the first year of life. The half-life of maternal antibodies targeting a range of different pathogens is approximately 30 days (10). The age at which infants become susceptible to different infections is therefore largely dependent on the specificity and titer of maternal antibodies received at birth, as the rates of waning are consistent across geographical regions (11). As a rule of thumb, maternal antibodies generally wane to ineffective levels around 6–9 months of age. This means that when infants typically start attending childcare settings, protection from maternal antibodies is likely to be negligible.

Increased susceptibility following maternal antibody waning is evident in exemplar exanthematous, respiratory, and enteric infections. Considering first an examthemous infection, maternal antibodies to human herpesvirus 6 (HHV6, causative agent of roseola) reach their nadir around 6 months of age, and then, antibodies detected in infants start rising again from ~8 months to ~14 months of age when infants are exposed (12). This coincides with when many children will be starting childcare as parents return to work from maternity/parental leave. Infection is almost universal by 36 months of age. Maternal antibodies are an important aspect of protection of neonates against respiratory syncytial virus (RSV), with IgG titers against both pre- and post-fusion F protein highest at 1–2 months after birth, and declining to their lowest level (mean) at 9–10 months of age, before rising again as a result of natural infection, leading to autochthonous IgG responses (13). Studies evaluating maternal antibody waning to common gastrointestinal pathogens are generally from low-middle-income countries and show waning to unprotective levels by 6–8 months (14).Reports from high-income countries are limited, but recent data indicate that maternal antibodies specific for rotavirus can wane to unprotective levels by around 3 months of age (15). As such, children, and especially infants, entering childcare do so from a position of immune naivety, with consequences for onward transmission (Box 1).

BOX 1. INFLUENZA, SARS-COV-2, AND TRANSMISSION FROM IMMUNE-NAIVE HOSTS

The degree of immune naivety may be particularly important for the propensity of children to transmit endemic pathogens compared to novel infectious diseases. Multiple countries have programs offering children aged 2 and above vaccination with live-attenuated influenza vaccine (e.g., FluMist [16]) to reduce disease and importantly to limit onward transmission from this immune-naive population to immunocompromised adults and peers. As with influenza, children are also a common source of endemic coronavirus transmission to adults. In contrast, studies of the epidemiology of SARS-CoV-2 during the earlier stages of the pandemic did not find a link between the presence of young children in a household and adult risk of SARS-CoV-2 (17), and the rates of infection are lower in children under the age of 5 than in children of older ages (18). This demonstrates that when infection history and adaptive immunity do not differ between adults and children (e.g., equally immune naive to an emerging virus), children can be equally efficient at viral control. Comparing just two respiratory pathogens, it is clear that the risk of transmission (between young or from young children to adults, who may be immunocompromised) and the risk of disease vary significantly from pathogen to pathogen, with prior exposure being a key factor.

Unlike maternal antibodies, cellular immunity is not passively transferred from the mother to the child, but it is *de novo* generated as children encounter pathogens. The infant's cellular immune response is also different from that of older children. In addition to possessing immune cell populations that are distinct from adults (19), the frequent exposure of infants and children to new antigens, from the moment of birth, drives absolute and relative changes in lymphocyte numbers and composition. Both B and T cells are activated by new antigens, proliferating in response to pathogens and maturing toward longer-term memory responses. This leads to a notable increase in absolute lymphocyte numbers.

Figure 1 demonstrates antibody dynamics and lymphocyte subsets from age 0 to 24 months.

There is an inflection point in lymphocyte profiles around age 2 toward more adult-like absolute lymphocyte numbers and lymphocyte proportions (21). Changes also occur in the first 2 years of life to the nature and quality of the immune response, with key case studies characterizing the cellular immune response to vaccines and viral infections. For example, infants who received the live-attenuated combined measles-mumps vaccine at 6, 9, or 12 months had lower Th1 (IFN-γ) responses to both measles and mumps, compared to those receiving the vaccine at 15 months or older (22). Infants aged 6–12 months also make lower IFN-γ responses to mRNA SARS-CoV-2 vaccines than adults (23). IFN-γ responses to RSV appear in infants and children after a single season but are an order of magnitude more frequent (a 10-fold increase in IFN-γ PBMC

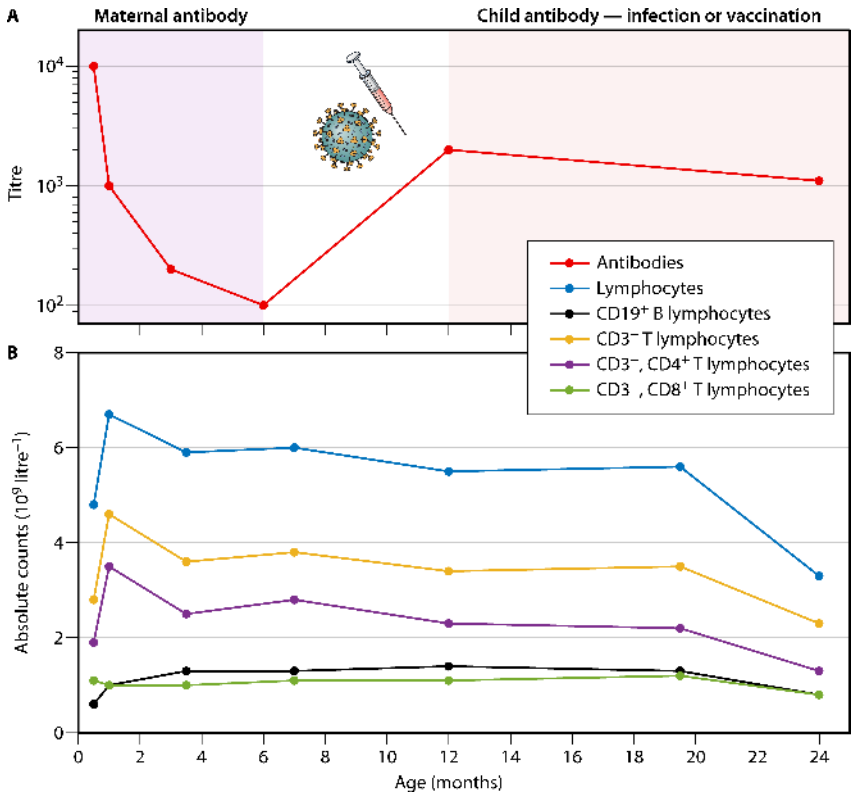


FIG 1 Humoral and cellular immunity in the first 2 years of life. Graphs showing example dynamics of maternal and child antibody responses in the first 24 months of life (sample titer data adapted from reference 20) (A) and average lymphocyte counts in the first 24 months of life (adapted from reference 21) (B). In A, infants receive maternally-derived antibodies to the measles virus *in utero*. Antibody titers decline over a period of months (shaded purple) until the child is either infected or vaccinated at age 12 months. At this point, antibody titers increase (shaded orange) as durable immunity is generated by the child's own immune system. In B, mean absolute lymphocyte counts are shown from 2 weeks to 24 months of age. In contrast to antibodies, no cellular immunity is derived from the mother.

responses as measured by ELIspot) after several seasons of repeated exposure in children aged 2 and older (24). In short, the infant cellular immune response is of a different quality to that of adults, whether considering stimulation via natural infection, live-attenuated viral vaccines, or mRNA vaccines.

Infants and children differ from adults in important aspects of their innate immune responses. After 6 months of age, the levels of complement are close to those of adults, and expression of complement receptors increases with age too; this benefits older infants and toddlers experiencing secondary infections (and immune exposures after vaccination), who are recalling antibody responses from immune memory (25). Innate immunity encompasses pathogen recognition via Toll-like receptors, which is a key part of the signaling cascade triggering innate immune cell activation. However, TLR signaling of cytokine expression in children, even at age 5, is not as robust as in adults —for example, interleukin-12 production does not fully mature until age 12 (26). The wider pattern of cytokine expression in response to pathogen stimulation takes time to reach adult-like profiles and varies from the neonatal period into childhood (27). The innate immune cell profile evolves from infancy into the toddler years and beyond, with neutrophils, monocytes, and macrophages all differing in function in infants compared to adults, with some evidence of diminished alveolar macrophage function in toddlers up to the age of 2 (28). NK cells, even if present in similar numbers, differ between children and adults; NK cells can display a range of activating and inhibitory receptors on their surfaces, and these change from infancy through to adulthood, with immunological consequences that are not fully understood (25, 27). Differences in innate immune function are thought, alongside immune naivety, to contribute to influenza A virus (29) and RSV (25, 30) infection severity in infants and children. In contrast, the rapid induction of innate antiviral responses in children may be a protective factor against more severe SARS-CoV-2 disease compared to adults (31).

In summary, the innate, antibody-dependent, and adaptive cellular immune responses of infants and toddlers below 2 years of age are still quantitatively and qualitatively different from those of both older children and adults. This varies on a pathogen-by-pathogen basis (32) but is a key component of the susceptibility of infants and small children to a variety of infectious diseases.

EPIDEMIOLOGY OF RESPIRATORY, GASTROINTESTINAL, AND EXANTHEMATOUS INFECTIONS IN INFANTS AND TODDLERS

Parents facing another bout of infection, be it respiratory, febrile, or diarrheal, may find themselves wondering, "Is it normal for my child to be ill so often?" To address this, we must consider why infants and young children are more susceptible to infectious diseases than older children. There are a range of reasons (33), including the following:

- Immature immune systems and immune naivety (as discussed above).
- Poor personal hygiene.
- Fecal incontinence.
- Mouthing behaviors (seeking to put things in their mouths)

Most infectious diseases contracted in a childcare setting are mild and can be managed at home, but they still have an impact on the child and their parents and caregivers. Articles with titles like "Help! My Kid Started Nursery, And Now They're Always Sick" (34) will strike a chord with many parents of young children. It is therefore useful to contextualize the range of "normal" for episodes of different types of illness experienced by children when they begin childcare.

Respiratory infections

Table 1 provides the respiratory infection/illness episodes by age.

The perception of frequent illnesses in infants and children under 5 years is backed by evidence: under-fives test positive for a respiratory virus 50% of the year on average,

TABLE 1 Common respiratory pathogens causing influenza-like illness

Pathogen and pathogen type	Epidemiological data on age at first infection and seroprevalence by age	Reference(s)
Influenza A virus (-ssRNA virus)	Age at first infection highly variable by season and subtype	(35)
	Influenza A(H1N1) 12 months	
	Influenza A/H3N2: attack rate highest between 2 and 4 years old	(36)
	All children seroconverted to at least one influenza A lineage by age 7	(36)
Influenza B virus (-ssRNA virus)	Age at first infection: 13 months	(35)
	72% seroconverted to at least one flu B lineage by age 7	(36)
Respiratory syncytial virus (-ssRNA virus)	Age at first infection: 19 months[d]	(37)
	60% of children infected by first birthday	(38)
	53% of children are seropositive by age 1	(39)
	Maternal antibodies decline up to 10–12 months of age; 60% of children have evidence of a recent primary infection (IgA) by age 1	(13)
Seasonal coronaviruses (+ssRNA viruses)[a]	17 months[d]	(37)
Rhinoviruses (+ssRNA viruses)	3 months[d]	(37)
Adenoviruses (dsDNA viruses)	24 months[d]	(37)
Parainfluenza viruses (-ssRNA viruses)[b]	23 months[d]	(37)
	Varies by species and genotype, children under 1 most affected (UKHSA data)	(40)
	Laboratory surveillance data suggest that PIV rates may be highest for those under 1	(41)
Metapneumovirus (-ssRNA viruses)	6–12 months (median 6 months, mean 12 months)	(42)
Bocaparvovirus[c] (ssDNA virus)	16 months[d]	(37)
	1–2 years	(43, 44)

[a]229E, NL63, OC43, and HKU11.
[b]Parainfluenza viruses include four paraphyletic species, not always distinguished by species or type in publications. HPIV-1 & HPIV-3 are members of genus Respirovirus and HPIV-2 & HPIV-4 members of genus Rubulavirus.
[c]HBoV1, associated with RTI and wheezing (43).
[d]Median age at first positive swab.

working out at an average of 12 episodes per year. Eight to nine of those episodes are symptomatic, which could be envisaged as a cold almost every month (45). Other studies estimate that children aged 15 months experience ~one acute respiratory infection per month (37).

These frequent respiratory infections, predominantly viral, are driven by immune naivety, waning maternal antibody protection, and the number of diverse viruses capable of causing respiratory symptoms. The age at primary infection for multiple human respiratory viruses overlaps with the age at which many infants and toddlers are first attending childcare outside the home (Table 1). Studies from high-income countries such as Germany, Netherlands, USA, and Australia paint largely similar pictures: rhinoviruses are typically the first respiratory pathogens by which infants are infected, and infants and toddlers then progress through primary infections with a range of viruses, many of which have multiple species or serotypes (parainfluenza, adenovirus, and rhinovirus) or which are prone to seroreversion (waning of antibodies to undetectable levels) and reinfection (seasonal coronaviruses [46], SARS-CoV-2 [47]).

Few studies test for all these pathogens in a single cohort or population, and the mixture and relative proportion vary with factors such as season, age, and location. The data for age at first infection in Table 1 are derived from a mixture of seroepidemiology studies, national surveillance data, and prospective swabbing studies from high-income countries because consistent data for a single country were not available. Nonetheless, these patterns are likely to be correlated with the duration of maternal immunity to specific pathogens and/or the specific force of infection of each pathogen.

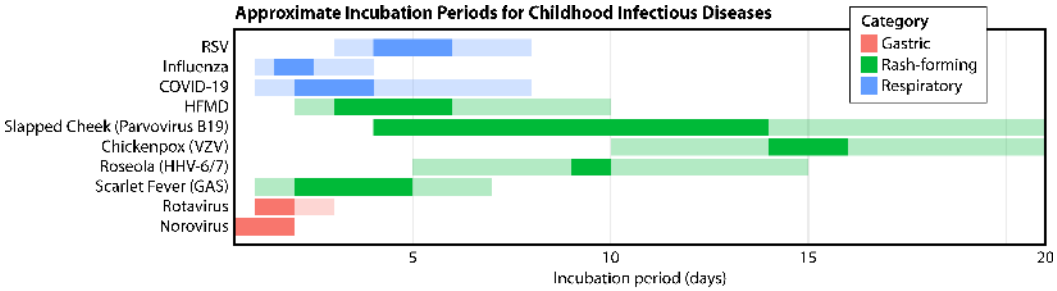
SARS-CoV-2 also infects and likely reinfects the 0–5 age group (48), but many studies report respiratory infection data from pre-2020, and thus, the impact of SARS-CoV-2 as part of the full influenza-like illness milieu is yet to be captured. Pre-pandemic data from Scotland (49) and New York City, USA (50) show that seasonal coronavirus infection is more common in toddlers and children under 5 years than in infants, although more data are required to gauge whether SARS-CoV-2 will fall into this pattern.

The pathogens in Table 1 have a diverse range of properties that help them succeed in transmitting in childcare environments. Adenoviruses benefit from features such as a high secondary attack rate (up to 67%), the ability to persist on surfaces as infectious fomites, and a relatively long duration of post-symptomatic shedding (up to several weeks in infants and young children). Rhinoviruses overcome immunity to previous infection in part through their extensive genetic diversity: five rhinovirus genotypes have been found to circulate in a single classroom in a 2-week period (51). Asymptomatic carriage is high, making policies that exclude children from childcare based on symptoms alone likely to be ineffective in preventing transmission (52). Similarly, presymptomatic transmission is also common (influenza, SARS-CoV-2, and RSV). As we discuss below, these features all make controlling the transmission of these many and varied pathogens challenging. Figure 2 shows the approximated incubation periods and transmission of a range of common childcare pathogens, including RSV, influenza, and SARS-CoV-2.

In summary, children under 5 years are frequently infected with respiratory viruses, more likely to test positive for a virus than older children and more likely to be symptomatic than older children. The perception by parents that toddlers are frequently ill with coughs and colds is supported by data (53). However, parents should take comfort that this will get better with time: the status quo of almost monthly respiratory infections improves with age. Children aged 5 and above have fewer days positive for a respiratory virus and are also less likely to be symptomatic than younger children (45). This is the result of repeated exposure to a range of respiratory pathogens, resulting in mature adaptive immune responses, both humoral and cellular. The specific impact of childcare attendance on respiratory infection epidemiology is discussed below.

Acute gastroenteritis

Acute gastroenteritis (AGE) infections, often known to parents as diarrhea and vomiting or D&V, are familiar childhood illnesses and are typically not distinguishable from one another based on symptoms alone. A Dutch study identified ~two cases of acute



Disease	Presymptomatic transmission	Asymptomatic presentation
RSV	Rare	42%
Influenza	1 day before symptoms	1–50%
COVID-19	Common, ~2 days prior to symptoms	36%
HFMD	1–3 days prior to symptoms	20–40%
Slapped Cheek (Parvovirus B19)	As much as a week	20–30%
Chickenpox (VZV)	1–2 days prior to symptoms	Rare
Roseola (HHV-6/7)	1–2 days prior to symptoms	Common
Scarlet Fever (GAS)	Up to 6 days	Up to 25%
Rotavirus	Rare	30%
Norovirus	Rare	21%

FIG 2 Incubation periods of common childhood diseases. Figure showing the incubation periods of 10 common childhood diseases. Darker colors indicate the likely window of transmission, with lighter colors giving the range that may include pre- or post-symptomatic transmission. Data on presymptomatic and asymptomatic transmission are summarized below the figure. Abbreviations: HFMD, hand foot and mouth disease; HHV, human herpes virus; VZV, varicella zoster virus; RSV, respiratory syncytial virus; and GAS, *Streptococcus* group A.

gastroenteritis per year in infants and children ≤4, compared to 0.8–1.4 cases per year in adults (54), emphasizing the disproportionate burden borne by children under 5 years of age.

Viruses are the predominant cause of acute gastroenteritis in children. Historically, rotavirus was the leading cause of AGE in children under 5 years. However, following the introduction of a live-attenuated oral rotavirus vaccine in the United States in 2006, and its subsequent adoption in most high-income countries, the incidence of rotavirus infection has declined substantially (55). In the UK, a 77% reduction in laboratory-confirmed rotavirus infections rapidly followed vaccine rollout (56).

The most common cause of viral gastroenteritis in children under 5 years of age is now norovirus. Approximately 15% of children in this age group experience norovirus-associated AGE each year (57), and norovirus is responsible for 20%–25% AGE cases presenting to healthcare settings in this age group (58). This highlights the significant contribution made by norovirus to the pediatric AGE burden in high-income regions. There is currently no vaccine available for norovirus, and although progress has been made with vaccine candidates based on virus-like particles, a recent phase IIb clinical trial in infants 4–6 months old did not show encouraging efficacy (59). Sustained immunity to symptomatic norovirus is complicated by the existence of multiple genotypes, with only some degree of heterotypic protection provided by previous infections. As a result, reinfection of children between the ages of 2 and 5 years is common as their relatively naive immune systems are exposed to a wider range of circulating genotypes (60).

In addition to rotavirus and norovirus, several other viruses are known to cause AGE in young children, although their precise incidence is less well defined due to limited routine testing and underreporting. Notably, astrovirus and sapovirus, both non-enveloped, single-stranded RNA viruses, have been implicated in sporadic cases and outbreaks of pediatric AGE. These viruses tend to cause milder illness compared to rotavirus or norovirus but can still contribute to the overall disease burden, particularly in infants and toddlers (61, 62). No vaccines are currently available for astrovirus or sapovirus, and their role in pediatric gastroenteritis may become more apparent if diagnostic testing becomes more widespread. Adenoviruses are also detected at a higher rate in infants with AGE compared to healthy controls (63).

While viruses are the most common cause of AGE in infants, bacterial pathogens can also play a significant role. Outbreaks involving *Salmonella*, *Shigella*, *Campylobacter*, and certain strains of *Escherichia coli* (*E. coli*) have been documented, and although less frequent, these infections are often associated with more severe symptoms or complications (64). In addition, the intestinal parasite *Giardia lamblia* can cause AGE in some contexts, but in high-income countries, the overall burden of *Giardia*-related disease is minimal compared to viral or bacterial causes and will not be considered further in this review.

Longitudinal and cross-sectional studies all highlight the frequency of enteric virus infection in healthy infants and children. A study of two infants from the UK, born in the 1980s, found that these infants shed enteric viruses in stool almost every day of their lives from 100 days after birth up to a year or more. Both infants were breastfed and did not attend out-of-home childcare during the period of study, had no diarrhea symptoms, and did not travel internationally (65). This is not unique: 40.8% of healthy children under 5 years were positive for at least one enteric virus in a study from three US locations (63). Thus, frequent prolonged shedding of a range of viruses is the norm even without the added transmission of enteric viruses taking place within a childcare environment.

Table 2 summarizes our knowledge of the age at first infection for common enteric viruses associated with acute gastroenteritis in infants and children.

Children themselves are at risk of primary infections with AGE pathogens, but they also increase the risk of household members contracting these infections. The secondary attack rate for household members may exceed 20% (70). Given how little virus it takes to cause infection (71, 72), and the high likelihood of being in close contact with bodily fluids, parents and carers can be considered "sitting ducks." This is further

TABLE 2 Acute gastroenteritis episodes by age

Pathogen and pathogen type	Epidemiological data on age at first infection	Reference(s)
Norovirus (+ssRNA virus)	50% medically attended cases were 6–18 months (mean 17 months)	(58)
	Median 13.8 months	(66)
Rotavirus (dsRNA virus)	6–24 months, with a median age of 15 months in high-income countries[a]	(15, 67)
Astrovirus (+ssRNA virus)	6–18 months, likely by age 2	(53, 68)
	Median 17.6 months	(66)
Sapovirus (+ssRNA virus)	5–24 months	(69)
	Median 14.3 months	(66)

[a]Live oral-attenuated vaccines were introduced in the US in 2006 and in the UK in 2013; these are highly effective at reducing severe gastroenteritis in these regions.

exacerbated by the high environmental stability of most enteric pathogens (norovirus and rotavirus are both non-enveloped viruses) and asymptomatic shedding. A 5-year retrospective study of household AGE incidence in the UK found that the presence of a child under 5 increases household AGE risk ratio by >6 compared to households without an under 5-year-old child (73). In the first 21 weeks of the 2024/2025 season, recorded norovirus infections in the UK were double the 5-year average and led to ward closures in several cities due to overcrowding. These data demonstrate the wider impact childhood infections can have on public health resources (74).

Rash-associated illnesses: exanthems and dermatological infections

The third category of infections we will consider is those which cause rashes (exanthems) typically seen in infants, toddlers, and children, although adults may also be susceptible if primary infection is delayed or the adult is exposed to a new genotype. These infections may also cause non-specific febrile symptoms that cannot clearly be associated with respiratory or gastrointestinal disease. We also consider here selected dermatological infections that parents may confuse with viral exanthems. Examples of rash-associated infections, exanthematous and erythromatous, include chickenpox, hand, foot, and mouth disease (HFMD), and scarlet fever, caused by a double-stranded DNA virus, RNA viruses, and gram-positive bacteria, respectively (Table 3). These pathogens can cause diverse symptoms such as respiratory symptoms, fever, and diarrhea and may be spread by respiratory, close contact, or fecal-oral routes. The relative distinctiveness of the exanthems or dermatological manifestations caused often allows these infections to be diagnosed clinically and for affected individuals to be excluded from childcare, according to specific public health guidelines. We present the UK Health Security Agency (UKHSA) guidance in Table 4 as an example of public health exclusion periods for common infant and child infections.

Fewer prospective studies have been carried out for rash-associated pathogens of infants and children than for infections with primarily respiratory or enteric symptoms, perhaps because those diseases associated with some of the highest morbidity and mortality can be prevented or ameliorated by vaccination (e.g., measles and rubella). By combining data from symptomatic surveillance, molecular diagnostics, and seroepidemiology, we can form a general picture of the age at first infection for the pathogens in Table 3. Many childcare settings will have fever exclusion policies or other infectious disease policies that are likely to exclude a child with the infections in Table 3. For example, a UK childcare setting (Childbase Partnership) has an Infectious Diseases policy document, which states that a child must be well to attend, defining well to include "A child who is not reliant on temperature relief medication." Moderate-to-high fever is a common symptom of many of these infections. Before reaching the age of formal schooling in the UK, many infants and children will be at risk of contracting a range of these pathogens.

One of the exanthematous illnesses associated with the earliest age at first infection, and common in childcare-age infants and children, is roseola. This is associated with three of the four human betaherpesviruses, HHV6A, 6B, and 7. HHV-6B is the most common roseola agent, and all three of these viruses are spread through salivary

TABLE 3 Rash-associated infections (exanthems) and dermatological infections[a]

Disease, pathogen, and pathogen type	Epidemiological data on age at first infection	Seroepidemiology	Reference(s)
Chickenpox Varicella-zoster virus (HHV3) dsDNA virus		65% of children have seroconverted by age 5	(75)
	General practice (GP) [UK primary care] consultation rates for varicella are highest in age 1–3 yr; median age of GP consultation varies by ethnicity: 2.8 yr for white children, 4.2 yr for Black children, 4.5 yr for children of Afro-Caribbean ethnicity		(76)
	COVID-19 pandemic may have reduced the age of primary infection (inference from general practice consultations)		(77)
		Born in Bradford cohort: 10% seropositive by age 1, 23% of white children in Bradford at age 2 but 14% of children of Pakistani ethnicity in Bradford at age 2	(78)
Slapped cheek Parvovirus B19 ssDNA virus		Maternal antibody wanes up to 11 months; seroprevalence increases again after 11 months	(79)
		Peak force of infection ages 7-9 across Europe	(80)
Exanthem subitum/roseola Human herpesviruses 6A, 6B, and 7 dsDNA viruses		Seroprevalence climbs during first year of life and suggests infection occurs for many children between 6–12 months (seroprevalence 23% at 2–6 months; 69% in 6–12 month group)	(81)
	PCR-based studies see incidence peak between 9 and 21 months		(82)
		HHV6B infection likely slightly earlier than HHV6A	(83)
		HHV7 also causes seroprevalence to rise sharply between 12 and 24 months	(84)
		Median age for HHV6: 9 months, median age for HHV7: 26 months	(85)
		HHV6 seroconversion occurs in the majority of infants before 1 year; infection occurs more gradually for HHV7 between ages 1 and 2 and later	(86)
		HHV6: 85% seropositive between ages 1 and 2 (USA, 1990)	(87)
Hand, foot, and mouth disease (HFMD) Coxsackievirus A16, Enterovirus 71, other enterovirus types +ssRNA viruses	Mean age of cases in French 2021 outbreak: 2.09 years; similar to 2014		(88)
	GP consultations from the UK, pre- and post-pandemic, show incidence rates 50%–100% higher per standardized 100,000 people among 1–4 age group than under 1s, but both groups are an order of magnitude more likely to visit the GP with HMF symptoms than any other age groups		(89)
		Maternal antibodies wane between 6-11 months and rise from 1 year onwards	(90)

(*Continued on next page*)

TABLE 3 Rash-associated infections (exanthems) and dermatological infections[a] (*Continued*)

Disease, pathogen, and pathogen type	Epidemiological data on age at first infection	Seroepidemiology	Reference(s)
		Modeling (pre-pandemic serology) suggests EV-A71 40%–60% of children seropositive by age 4 and CVA6 60-70% seropositive by age 4	(91)
Scarlet fever/scarlatina *Streptococcus pyogenes* (group A strep) Gram-positive bacterium	Median age: 4 years		(92, 93)
Impetigo[b] *Staphylococcus aureus* or *Streptococcus pyogenes* Both gram-positive bacteria	Majority of cases in children under the age of 7		(94)
	Children aged 1–4 have highest incidence rates		(95, 96)

[a]HHV-7 also causes roseola in older children (97), but with a lower burden of disease than HHV-6B.
[b]Impetigo is a dermatological infection.

shedding and cause lifelong infection. HHV-6B primary infection is particularly associated with high fever (≥40°C); some studies estimate the median age of infection is 9 months, while HHV-7 has a median age of infection of 26 months (85). As such, roseola may be one of the early febrile/exanthematous illnesses in an infant or child attending childcare contracts, and reactivation of these viruses may also cause pityriasis rosea, a viral rash sometimes mistaken for a fungal skin infection.

Other rash-forming illnesses cause outbreaks in childcare settings but typically infect slightly older children parvovirus B19, HFMD-associated enterovirus and coxsackievirus serotypes, and scarlet fever caused by group A strep (Table 3). VZV shows epidemiological patterns where ethnicity strongly influences the age at first infection, with both seroepidemiology and primary care (general practice [GP]) consultation data showing a trend for children of white ethnicity in the UK to be infected at an earlier age than children of Asian (78), Afro-Caribbean, or Black ethnicity (76). The age of VZV infection has also been perturbed by the SARS-CoV-2 pandemic, with increased chickenpox cases in infants compared to pre-pandemic. It is unclear whether this is an acceleration of a trend already occurring in the UK since the 1980s, or whether this is a temporary change caused by pandemic restrictions in the UK in 2020–2021 (77). National vaccination programs need to take account of variations in the population at risk of VZV when designing vaccine schedules, balanced against the optimal timing of doses to achieve long-term immunological protection.

There are also complex interactions between some of these infections. Epidemiology shows a relationship between primary VZV infection and a subsequent increased risk of scarlet fever (including the most severe forms of invasive group A strep disease [98]). Although scarlet fever typically affects school-aged children in the UK (i.e., over 5 years old), outbreaks have been reported from childcare settings in the UK and Spain (92, 99), and transmission can occur from older to younger siblings, fueling onward transmission (100). Household contacts have a much higher risk of group A strep disease after a household scarlet fever case. Asymptomatic child carriers also seem capable of transmitting to their peers, making outbreak control difficult if it is based on excluding only symptomatic children (100).

Other pathogens can cause dermatological infections in children, which may be recognized by parents as a rash, and several of these are known to spread in childcare settings. Impetigo, for example, is a common dermatological infection of childcare settings. It is a highly contagious bacterial skin disease that causes pustules and honey-colored erosions and is more likely to cause systemic symptoms of fever, malaise, and lymphadenopathy. It is typically caused by *S. aureus* or *S. pyogenes*. In general practice, children under the age of 7 represent most cases (101), and for non-bullous

TABLE 4 UKHSA exclusion periods for common childcare infections, United Kingdom

Infection	Exclusion period	Comments
Chickenpox (varicella zoster virus)	5 days minimum from rash onset; all blisters must have crusted over	Vaccine preventable (two doses of varicella vaccine/MMRV)
Respiratory infections including COVID-19	Exclusion on the basis of high temperature and if the child feels unwell; specific COVID-19 exclusion period: 3 days after a positive test; testing is not routinely recommended.	An affected child can continue to attend if symptoms are mild (such as a runny nose or headache)
Diarrhea and vomiting (gastroenteritis), including rotavirus and norovirus	48 hours after resolution of diarrhea and vomiting	Rotavirus is vaccine preventable; additional exclusion periods are required if specific pathogens are identified, e.g., hepatitis A
Influenza (or influenza-like illness)	Until recovered (see "Respiratory infections," above)	Outbreaks should be reported to the local health protection team
Hand, foot, and mouth disease (HFMD)	None	Outbreaks should be reported to local health protection teams if a large number of children are affected; virus is shed in feces for a few weeks after the rash[a]
Impetigo (typically *Staphylococcus aureus* or *Streptococcus pyogenes*)	48 h after starting treatment (antibiotics and/or hydrogen peroxide cream)[a], or until lesions are crusted or healed	Antibiotic treatment reduces the period of infectiousness and speeds lesion healing
Measles virus	4 days from rash onset and well enough to participate	Vaccine preventable (two doses of MMR/MMRV); outbreaks should be reported to local health protection teams[a]
Rubella virus	5 days from rash onset	Vaccine preventable (two doses of MMR/MMRV)
Scarlet fever (*Streptococcus pyogenes*)	24 h after starting antibiotic treatment	If antibiotics are declined, exclusion until resolution of symptoms
Slapped cheek/ Parvovirus B19	None after rash development	

[a]https://www.gov.uk/government/publications/health-protection-in-schools-and-other-childcare-facilities/managing-specific-infectious-diseases-a-to-z.

impetigo, the rates are higher in children aged 1–4 than in either older or younger age groups (95). Marginalized communities in high-income countries seem particularly at risk from impetigo, a further example of the epidemiology of childhood infections intersecting with race, class, and income level (94).

While public health bodies may not necessarily require or recommend exclusion for specific illnesses (Table 4) because the symptoms of one pathogen may mimic another, exclusion from childcare may occur because accurate diagnosis cannot be obtained in a timely manner.

In cases of respiratory, gastrointestinal, and exanthematous illnesses, many pathogens can be transmitted both presymptomatically and/or asymptomatically, making it hard to prevent or break transmission chains (Fig. 2). In fact, all of the childhood infections considered here show some propensity for presymptomatic or asymptomatic transmission, and in some cases, this can be substantial. Parvovirus B19 (slapped cheek) is a notable example, as it may spread as much as a week prior to the onset of any symptoms and is typically non-infectious at the point of the characteristic facial rash. Others, such as RSV and rotavirus, can have high rates of asymptomatic carriage—properties which together challenge efforts to control infections through exclusion guidance alone (Table 4). Incubation times can also be prolonged: chickenpox (VZV), for instance, can take 10–21 days between contracting the infection and symptom onset. This means that even when exclusion rules and additional cleaning measures are strictly applied, keeping outbreaks under control is difficult. In addition, prolonged viral shedding after symptom resolution, particularly for gastrointestinal pathogens, further extends the window of possible transmission beyond the period when a child is actively unwell.

Taken together, these properties of childhood pathogens, when combined with close contact and imperfect hygiene in childcare settings, create conditions highly conducive to sustained transmission. This leads us to consider what amplifying effect attendance at childcare may have on the epidemiology of these infections.

IMPACT OF CHILDCARE ON RISK OF CONTRACTING INFECTIOUS DISEASES

Respiratory infection and childcare

As discussed above, high rates of respiratory infection are common in early childhood. Infants and children experience primary infections and subsequent reinfections as they build a robust humoral and cellular immune response to a variety of respiratory pathogens. In a longitudinal community-based birth cohort study in Brisbane, it was estimated that in the first 2 years of life, children experience at least 13 discrete respiratory tract infections, peaking at the age of 15 months, where the rate was over one acute respiratory tract infection per child per month (37). This incidence is likely increased by attendance at early childcare settings, which may amplify exposure. For instance, in a Dutch study including 1,827 children under the age of 24 months, initiation of center-based childcare was associated with a substantial increase in respiratory symptoms, with the mean number of days with illness rising from 3.8 in the month prior to childcare attendance to 10.6 at 2 months post-initiation, remaining elevated for at least 9 months (102). Similar findings have been reported in the UK, where respiratory viral burden in 220 infants was assessed through oropharyngeal swabs (103). Here, both attendance at childcare and exposure via siblings resulted in a significantly higher burden of detected respiratory pathogens, with attendance at childcare also associated with a higher prevalence of co-detection of viral and bacterial pathogens in the first 2 years of life. In a prospective household cohort study assessing the prevalence of 9 respiratory viruses using PCR, it was found that children in childcare have increased odds of infection with adenovirus and human metapneumovirus. The pool of detected viruses associated with childcare respiratory infections was found to be significantly richer and more diverse than in children cared for at home (104). It is likely that the increased opportunities for close contact and shared airspace in childcare environments create ideal conditions for viral spread, resulting in respiratory infection rates above the already high baseline seen in young children.

This elevated risk encompasses both mild and more severe respiratory outcomes. Population-based registry analyses in Danish children aged between 0 and 5 have shown that the rates of inpatient hospitalization for respiratory infections are higher among children attending group childcare relative to those cared for at home (105). This was as high as a 69% higher incidence of acute respiratory infections requiring hospitalization in children under the age of 1. The contribution of childcare exposure to RSV epidemiology is particularly pronounced. In the Born in Bradford cohort (UK), it was found that over half of children were seropositive for RSV by age 1, and formal childcare attendance was associated with a 36% increased risk of RSV infection in infancy (39). High rates of prevalence are also observed for influenza, rhinovirus, and seasonal coronaviruses, which are frequently implicated in childcare outbreaks (106).

Enteric infection and childcare

Several studies have examined the impact of childcare attendance on the risk of AGE, consistently highlighting increased susceptibility, particularly in younger children. Lu et al. reported that children in formal childcare settings had a 1.6–2 times higher risk of developing mild AGE compared to those cared for at home, with the risk being greatest at younger ages (107). Hullegie et al. (108) identified a similar trend by analyzing Dutch health records; a slight increase in AGE incidence during a child's first year in formal childcare, with an incidence rate of 1.13 relative to non-attendees. However, Kamper-Jørgensen et al. offered a reassuring counterpoint from Denmark, showing that while childcare attendance may increase mild infections, it did not raise the risk of hospitalization for gastroenteritis in infants (109). Another study of childcare attendees from Denmark found that while testing positive for an enteric virus was a frequent event (over a third of all stool samples, from symptomatic and asymptomatic children), children aged 3–6 are half as likely to test positive for an enteric virus compared to children aged under 3 (110). Thus, age is a protective factor against AGE in childcare attendees.

An important consideration regarding the impact of increased risk of AGE in infants and children attending out-of-home childcare is the increased risk of AGE in caregivers and household members. Pijnacker and colleagues showed that adults aged 25–44 had an odds ratio of 2.8 for AGE if they lived with children who attended out-of-home care versus 0.7 if they lived with children cared for at home (reference population: adults of the same age with no children living at home) (54). A norovirus outbreak investigation from a childcare center in Australia found that, on average, each symptomatic infant or child infected a further child or staff member at the childcare center and also a family member, with a household secondary attack rate of 36.5% (111). The mixing of infants and children of different ages at childcare centers, as well as the mixing of siblings within the home (112), helps AGE pathogens spread even more successfully than might already be the case and impacts adult caregivers in both the childcare and home settings.

Exanthematous illness and childcare

Many viral infections and some bacteria can cause an exanthem or dermatological infection in addition to other symptoms. Often, these rashes are not characteristic enough to identify the exact causative pathogen, but it is important to make sure that it is not part of a serious infection, such as meningococcal infection. Outbreaks of exanthematous illnesses are common in childcare settings where transmission is enhanced by close contact for 10–12 h per day.

Although rashes and dermatological infections in children are relatively common, outbreaks of viral exanthems in childcare settings are not surveyed in the same way as primarily respiratory and gastrointestinal illnesses. This may be because of the varied infectious and non-infectious causes of rash in infants and young children. However, there are notable case studies of the impact of childcare attendance on the epidemiology of three viruses: VZV, HHV6, and EV-A71 (HFMD).

A cross-sectional study of primary VZV infection conducted in Germany in over 17,000 1- to 17-year-old children found that, alongside increasing age and the presence of older siblings in the household, starting childcare at younger ages was significantly associated with VZV seropositivity. In children not yet of school age (≤5 years), those that started to attend childcare aged under 1 had an odds ratio of 1.6 (CI: 1–2.5), and children starting childcare aged 1–2 an OR of 1.6 (CI: 1.1–2.2) compared to 0.9 (CI: 0.7–1.2) in those that started childcare settings age 3 and above (reference population: only children aged between 1 and 6 years) (113).

As well as transmission within households, HHV-6 (both 6A and 6B) can be transmitted in childcare settings. A study of 730 children in eight childcare centers in Brazil found that over 20% of children were affected by outbreaks of fever with and without exanthem between October and December in a single year; 64% of serum samples tested for HHV-6 antibodies showed an immunoglobulin M (IgM)+/IgG+ seroresponse. HHV-6 DNA was detected in plasma and lymphocytes of 26 individuals, suggesting that primary infection was occurring during these outbreaks. No genetic epidemiology was performed; hence, it cannot be ruled out that children were infected at home, but as HHV6A and B are transmitted by saliva and respiratory droplets, outbreaks caused by direct child-to-child contact in childcare settings seem highly plausible (114).

HFMD is caused by several enterovirus genotypes, some of which are more severe than others. A survey carried out in Japan following an EV-A71 outbreak in 2000 examined the risk factors associated with 272 cases of complicated HFMD, defined as requiring hospitalization or fatality. More severe cases with fatalities, long-term sequelae, and hospitalizations over 7 days were compared with less severe cases that did not meet these criteria. The proportion of children attending childcare centers was significantly larger in the group with more severe cases (35% vs. 25%), and multivariate analysis showed a stronger association (OR: 2.96; 95% CI: 1.24–7.08). It is noted, however, that out of 96 more severe cases, 91 of these were classified due to prolonged hospital stays, which may mean that attending childcare centers itself is not the risk factor. It may be that the parents are unable to look after the children at home until they

are completely recovered, leading to longer hospital stays. Thus, the factors that lead children to attend childcare in the first place may also impact clinical treatment plans, in some countries, which may cause childcare-associated HFMD to appear more severe than might otherwise be the case (115).

ECONOMIC IMPACT OF CHILDCARE ILLNESSES

Looking after sick infants and children exacts a toll, in terms of well-being, lost educational opportunities, and losses to the economy (116). Economic losses are perhaps easiest to quantify, yet even here, the costs associated with childcare-associated illnesses are multifactorial (117, 118). In countries with universal healthcare that is free at the point of use, the costs of treating a sick child are often small (e.g., infant paracetamol for fever, emollients for skin reactions). The costs of lost productivity and lost educational opportunities can be more significant. Productivity losses include parents taking time off work to care for children; parents becoming sick themselves; children missing childcare that's already been paid for; and other adults (such as grandparents), who may themselves become sick, having to take time off to care for children and/or sick parents (119).

Recent estimates from the UK on the economic costs of chickenpox highlight that each day a child cannot attend childcare leads to a £170 loss of productivity for the parent (2024 costs) (120). Data from France emphasizes the impact of varicella infection: parents miss work, which has economic impacts, while children miss childcare or school (121), leading to lost days of play or learning.

Recent analysis of RSV in under-threes highlighted the economic impact on parents in England of time off caring for infants and children with respiratory tract infections. In this prospective surveillance study of children interacting with National Health Service (NHS) care and receiving a positive RSV test, parents lost a mean of 32.5 h of work (approximately 4 days) caring for their child. We might assume that milder cases of RSV, where parents did not interact with the NHS, may have been less severe and therefore may have resulted in fewer lost hours of work for parents, but this loss of work also applied to children and infants with a negative RSV test result (mean: 33.3 h). This suggests that many respiratory infections which are symptomatic enough for parents to seek healthcare advice or treatment for their children also lead to significant loss of work hours (122). Furthermore, child episodes of influenza-like illness (ILI) are associated with reduced parental quality of life. The reduction in quality-of-life scores was greater when the child's ILI was more severe (123). When we consider the impact of childcare-associated illnesses and appropriate interventions, the personal quality-of-life and financial implications for the whole family ought to be included.

We must also consider the impact of frequent infections on children themselves. There is some evidence that infection severe enough to result in hospitalization has a weak but measurable association with below-average numeracy and reading results, although this may be confounded by socioeconomic or other variables (124). Encouragingly, this suggests that if repeated illness is impacting children's educational development, it is a weak effect.

Childhood illnesses transmitted in the childcare environment also have implications for immunologically vulnerable populations, particularly pregnant women and immunocompromised family and caregivers. Many of the viral pathogens that infect infants and children, particularly parvovirus B19V, rubella, herpes simplex virus 1 (HSV-1), VZV, and cytomegalovirus (CMV), are TORCH (toxoplasmosis, others [syphilis, hepatitis B], rubella, CMV, and HSV1/2) pathogens (125) associated with congenital infections in pregnancy. Childcare workers are more likely than the general population to be women of childbearing age and have long been known to be at risk from primary infections with CMV and parvovirus B19V, which both carry risks of congenital disease during pregnancy (126). As we discuss below, vaccination protects children and their relatives and childcare professionals against VZV and rubella, while the hunt for effective vaccines for other TORCH pathogens is ongoing. Immune-compromised children or family members are more at risk of almost all of the infections discussed here; reduced

transmission would protect them indirectly. The immune naivety of infants and children impacts their infectiousness (Box 1), and thus, their transmission risk to immunocompromised individuals, in other ways. For example, children under 5 years will, on average, experience a longer duration of shedding of influenza virus (A or B), greater peak virus shedding, and more symptoms than older children or adults (127). This risk of onward transmission to immune-naive neonates and infants and immunocompromised contacts influences childhood vaccine recommendations in many countries.

Fully understanding the burden of disease and transmission potential for many pathogens of infants and children will require more routine use of molecular diagnostics or point-of-care testing (e.g., rapid antigen tests to confirm the agent and rates of community carriage); it is hard to define the scale of the problem, the age group most at risk, the pathogens causing greatest long-term impacts for the community and also children. themselves, without better data on infections driving child and parent time off childcare/work. These will be essential for designing effective future vaccination programs.

WHAT'S THE SOLUTION?

Vaccination

The infant and child vaccination program provides the chance to reduce the burden of disease for children in childcare by averting and/or ameliorating infection, rather than simply delaying it (128). The current childhood vaccine program in the UK includes the six-in-one vaccine (Diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type b [HiB], and hepatitis B), Meningococcal group B, and C, Rotavirus, Pneumococcal (13 serotypes), MMR (measles, mumps, and rubella), and selective programs for tuberculosis, and maternal RSV and pertussis vaccination. In the UK, MMR became MMRV from January 2026 as vaccination against chickenpox joined the schedule. In this regard, the UK is behind many high-income countries by years or even decades (129). Figure 3 displays the current UK infant and child vaccination schedule, with additional details on other vaccines available elsewhere in the world or currently in development.

We note that many illnesses were not included in this review precisely because of the availability of effective vaccination (HiB, pertussis, and measles), which has substantially reduced both the morbidity and mortality burdens of these infections in the developed world, although both the US and UK have experienced domestic measles outbreaks leading to child fatalities in 2025, as vaccine coverage remains below the herd immunity threshold (132, 133). Increased uptake of maternal RSV vaccination and wider availability of monoclonal antibody immunization for RSV prevention may also ameliorate some of the morbidity burden of this infection, including in healthy, full-term infants and toddlers (122).

When introducing new vaccines into the childhood schedule, it is important to consider the cost-benefit analysis; therefore, it is essential to have accurate data on disease burden and vaccine efficacy. The VZV vaccines exemplify this; in 2009, the Joint Committee on Vaccination and Immunisation (JCVI) in the UK did not recommend childhood VZV vaccination. However, this decision was reversed in 2023 when subsequent studies identified higher rates of severe disease and serious secondary complications (e.g., bacterial infection of skin lesions and encephalitis). There was clear evidence from the CDC (Centers for Disease Control and Prevention) of the benefit of vaccination over the last 25 years in the USA, and no evidence of an increase in herpes zoster/shingles (which may have been an unwanted indirect impact of lowering varicella infections in the young reducing exogenous boosting of immunity in mid-late age for protection against herpes zoster [134]). This shifted the cost-benefit modeling significantly, leading to their recommendation to include two doses of VZV as part of MMRV (135).

For some childhood pathogens, vaccines have been employed elsewhere in the world. An inactivated alum-adjuvanted EV71 vaccine has been shown to be efficacious against HFMD and is used in China (136). A live orally-administered adenovirus vaccine

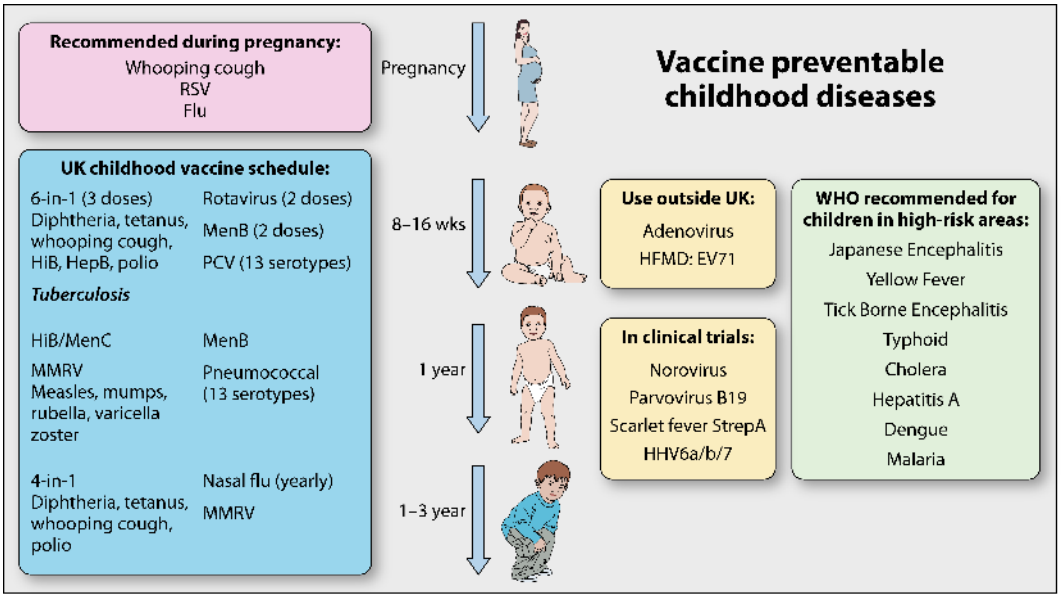


FIG 3 Vaccine-preventable childhood diseases. We include the vaccines that are currently widely licensed and recommended by the World Health Organization (WHO) during pregnancy (pink box: 130) and during childhood in the UK, as an example (blue box: UK childhood schedule from January 2026 [131]; white text shows selective programs in high-risk areas). Other vaccines that are used to target childhood diseases include those that are licensed in select countries outside the UK, that are in clinical testing, or that are recommended by the WHO in high-risk countries. Abbreviations: Flu, Influenza A; HepB, hepatitis B virus; HFMD, hand foot and mouth; HHV, human herpes virus; HiB, Haemophilus influenzae type b; MenB, meningococcal group B; MenC, meningococcal group C; MMRV, measles mumps, rubella, varicella zoster virus vaccine; PCV, pneumococcal conjugate vaccine; RSV, respiratory syncytial virus; Strep A, Streptococcus group A.

for types 4 and 7 has been employed historically and more recently reinstated for US military personnel (137). Although protection is only afforded to two types, this also shows proof of concept for an antibody-based vaccine to prevent adenovirus infections. There is proof of concept for a parvovirus B19 vaccine, with an effective canine parvovirus vaccine in use in the UK, and with evidence that passive transfer of antibodies can protect in cases of chronic anemia (138). Candidate vaccines, largely based on virus-like particles, have reached clinical testing for parvovirus B19 (139). Of the remaining common childhood infections, there are no licensed vaccines for non-EV71 HFMD, norovirus, parvovirus B19, HHV6A/B, HHV7, or group A streptococcus.

With the success of the rotavirus vaccine, norovirus has become the leading cause of childhood gastroenteritis in many developed countries; however, a vaccine against the six genogroups and >40 genotypes of human caliciviridae causing norovirus infections is challenging due to this diversity (140). Limited immune responses and poorly defined correlates of protection are also important reasons why we do not yet have an effective human norovirus vaccine (141). Ambitions to develop universal vaccines against human coronaviruses and influenza have also not yet been realized due to the difficulty of inducing cross-protective immunity for these variable viruses (142).

Herpes viruses are hugely complex viruses with complicated immune interactions. VZV is currently the only human herpesvirus with a licensed vaccine for use in infants. While progress with CMV vaccines often leads the way, little attention has been paid to HHV6A/B/7. As with HSV-1 (143) and VZV (144), nAb are the most likely mechanism to achieve protection from infection/disease, and tetrameric glycoprotein complex vaccines are in development (145).

Despite lifelong protection resulting from childhood primary infection with many of these pathogens, a mechanistic understanding of the immunological basis of this protection is lacking. Childhood infection does not, however, always lead to prolonged protection, which may reflect a high barrier to protective immunity or immune escape through constant evolution for some pathogens, particularly for RNA viruses.

There is much more we can learn about immune protection and immune evasion from studying effective immune responses during natural infection of children. How can children resolve this barrage of exposure to infectious agents, with the majority leading to little or no long-term impact, and also how can these childhood infections be so pervasive in the childcare setting? One way in which we can learn about protective immunity is through adult human challenge models, which allow the careful and controlled study of infections and to quickly assess vaccine efficacy, and these have been employed previously for parvovirus B19, group A streptococcus, and norovirus (146).

One legacy of the COVID-19 pandemic is the development of several platform technologies that are highly immunogenic, adaptable, and can be scaled globally. Developments in mRNA-based vaccines are likely to lead to effective vaccines against further childhood infections. A strep A vaccine global consortium (SAVAC) has been established, and recent success with mRNA vaccines has led to significant investment in a Moderna/Queensland University candidate (147).

As with all vaccines, inequalities in access and uptake rates limit the effectiveness of the childhood vaccines discussed above (148); an important way to limit the impact of childhood infections would be to improve vaccine uptake where vaccines are available and to learn from successful vaccination campaigns elsewhere in the world for vaccines that are not yet offered.

Role of breastfeeding in protection from infection

Many studies and meta-analyses have identified the benefits of breastfeeding for reducing infectious disease risk in infants and children (149–151). It is relevant to note here the benefits of breastfeeding against infectious disease reported in studies where infants in high-income countries were breastfed beyond 6 months. For example, breastfeeding beyond 6 months gives some protection against infectious gastroenteritis, AGE severe enough to require a healthcare diagnosis (151, 152). However, in the TEDDY study (152), breastfeeding was not protective against parent-reported gastroenteritis symptoms, which include milder symptoms that may lead to childcare exclusion but do not require interaction with a health care provider. Breastfeeding beyond 6 months also gives some protection against laryngitis and tracheitis, otitis media, and conjunctivitis; but in the 6 months and above age group, in the same study, they found continued breastfeeding to be associated with an increased risk of respiratory infection symptoms, including fever and common cold symptoms. It has been hypothesized that this is because breastfeeding prevents or delays respiratory infections in younger infants, which are then contracted by these infants at an older age. Several studies have found that protection against acute otitis media in ever-breastfed children continues after the cessation of breastfeeding, but this protection is reduced in older children compared to younger children (152, 153).

Interestingly, for maternal infections, breast milk may also provide antigens from the pathogen itself, for instance, in immune complexes; this antigen exposure could allow the newborn to make its own *de novo* immune response, which should be more long-lasting than passively acquired antibodies (154). This is just one example of how the infant-maternal immune interactions can be more complex than just the transfer of maternal antibodies, and a further example of what can be learned by studying infant immunity.

The odds ratios of various types of infection are smaller for breastfed infants (a proxy for decreased risk), whether exclusively or non-exclusively breastfed, under the age of 6 months—breastfeeding gives the greatest protection in younger infants (152). This protection reduces as infants and toddlers reach the age of entering childcare. Therefore, while mothers who can breastfeed should be supported to continue to do so for as long as they wish (in line with WHO guidelines), breastfeeding is not a magic bullet to prevent infections acquired at collective childcare settings.

Interventions in the childcare setting to reduce infectious disease transmission

Are there ways in which the *environment* of childcare settings can be altered to reduce the risk of disease transmission? Many governments gave public health advice on increasing access to fresh air to reduce respiratory virus transmission during the SARS-CoV-2 pandemic (e.g., UKHSA [155] and the CDC [156]). This builds on longstanding advice, and there have been attempts to quantify the effect of improved air quality on infection transmission within childcare settings specifically. However, evidence on the role of air quality and air cleaning to prevent or reduce respiratory illness in childcare settings is mixed. A comparison of two childcare settings, one of which was given mechanical air cleaners, found that there was a statistically significant difference in the number of days parents needed to miss work to care for their children over the 6-month study period, a relative reduction of ~30% (157). In contrast, a study using indoor CO_2 concentrations at childcare facilities as a proxy for air quality did not find an association between poor air quality (limited air exchange) and acute respiratory illness rates (158).

Public health bodies give broader advice on infection control in educational settings, including childcare (159, 160). This includes guidance on hand hygiene, cleaning, toileting, and disinfection of surfaces contaminated with bodily fluids. A study from the Netherlands reported that the odds of gastroenteritis outbreaks were reduced by cleaning child potties in designated waste disposal stations, use of chlorine-based cleaning products, and specific toy cleaning routines, for example, cleaning toys every day in conjunction with additional cleaning during outbreaks (161). Beyond the cleaning and disinfection recommended by public health bodies, research has identified that increased cleaning of childcare settings has costs as well as benefits. A study found that excessive cleaning product use while children are present can induce wheeze (162), while cleaning toys reduces detection of pathogens on surfaces but does not appear to reduce sickness absences or episodes of disease (163). Many interventional studies to improve hand hygiene in childcare settings include children aged 2 and above, but there is some evidence that hand hygiene programs for younger children in childcare settings can reduce acute gastroenteritis rates during periods of intense transmission (164), although not all studies find a significant benefit from hand hygiene interventions (165). Changing the environment of childcare settings to reduce infection seems intuitive, but research suggests it is difficult to effectively implement.

For a small number of infections common to childcare settings, antibiotics may be an appropriate infection control measure, reducing both the risk of long-term sequelae for the affected infant or child and also reducing the risk of onward transmission (Table 4). Scarlet fever (group A streptococcal infection) is a key example of a bacterial infection for which antibiotic administration is both a treatment and a transmission control measure employed in childcare settings. However, antibiotics are not suitable for many childhood infections, as the majority are viral rather than bacterial (Tables 1–3). When antibiotics are prescribed, or a bacterial infection is suspected, treatment often requires temporary exclusion from childcare, both to reduce transmission while the antibiotic takes effect and because childcare settings commonly require that the child has tolerated the antibiotic without adverse reaction before returning. Inappropriate or excessive antibiotic use can contribute to antimicrobial resistance (AMR), reducing the effectiveness of antibiotics over time (166). Inappropriate antibiotic prescribing in children is also associated with adverse events and increased healthcare costs (167). Nevertheless, antibiotics remain essential for bacterial childhood illnesses, including streptococcal pharyngitis (scarlet fever), bacterial pneumonia, urinary tract infections, otitis media, and some cases of bacterial gastroenteritis.

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Supporting working parents and caregivers as their children enter formal childcare

As the data from Tables 1–3 show, infants and children starting childcare can be expected to experience 12 respiratory, 2 gastrointestinal, and at least 1 exanthematous illness in their first year of attendance (Fig. 4). If one adds together all the exclusion periods recommended by UKHSA (Table 4), this would amount to 13 days off in total if a child experienced one bout of each illness (discounting measles and rubella as effective vaccination is available). This does not account for any parental time off for sickness following child-to-parent or sibling-to-sibling transmission.

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We feel that parents need more recognition from employers that both they and their children may be frequently sick following the return from parental leave and the beginning of formal childcare. Employers need realistic expectations that childhood infections are frequent and that this is normal; furthermore, employers need to recognize that within-household transmission of pathogens is often intense. Frequent illness is typically neither a reflection on the health status of the child or parent nor the cleanliness of the childcare setting.

Illness now or illness later?

Keeping infants at home longer before starting childcare is unlikely to be a solution to the problem of frequent infections. Although the incidence of respiratory infections peaks during the years before formal school age, there is some evidence that early exposure in group childcare settings may confer some protection in the early school years. The Tucson Children's Respiratory Study, which surveyed over 1,000 children enrolled at birth through to age 13, found that while children in large childcare settings had nearly twice the odds of frequent colds at the age of 2 compared to those cared for at home, by age 6–11 these children experienced fewer colds on average, presumably through acquired immunity (OR = 0.3–0.4 compared to children who did not attend large childcare settings) (168). The impacts on otitis media are similar.

The same is broadly true of gastrointestinal illnesses: a study of 2,220 infants and children from the Netherlands, followed over the course of 6 years, found that experiencing some childcare attendance in the first year of life (at least one half day per week) led to reduced gastrointestinal illness between ages 2 and 5 years (108).

Together, these observations suggest that many of these infections are postponed but not avoided by a delayed entry to childcare (Fig. 4). Parents can also be reassured that evidence suggests that even during the years of childcare attendance, the number

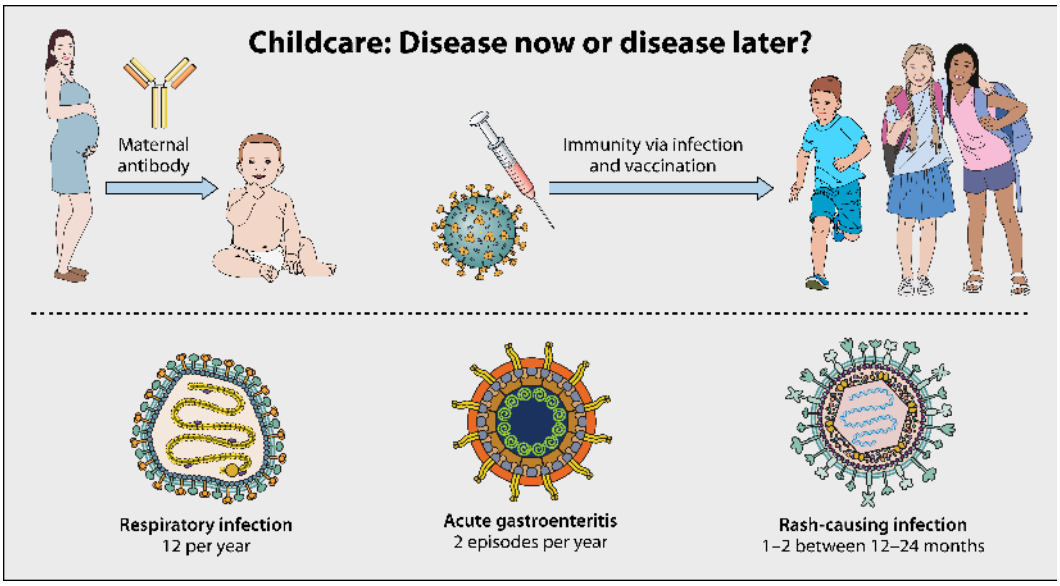

FIG 4 Childcare: disease now or disease later? Graphical summary of the transition from maternal to acquired immunity, and the expected burden of common infectious diseases for a 12-month-old child starting out-of-home childcare. In the top half of the panel, infants are born with maternal antibodies to a range of pathogens, but these wane during the first year of life and are replaced by the child's own adaptive immune responses as childhood continues. This immunity comes from vaccination and exposure to pathogens. Longitudinal and cross-sectional epidemiological studies of children who do and do not attend out-of-home childcare suggest that delaying entry to childcare delays, but does not prevent, exposure to the most common infectious diseases of the childcare environment. This can create a trade-off between illness in children of childcare age (i.e., 6 months to 4 years) and illness in older children when they reach the age of formal schooling (i.e., 5 years and above). In the bottom part of the panel, we show the approximate burden of respiratory (twelve) and gastrointestinal (two) infectious episodes a child of 12 months can be expected to experience in their first year of attending out-of-home childcare. They will also typically experience one to two infections that cause a rash (which may be a viral exanthem, erythematous rash, or dermatological infection).

of infection episodes decreases over time. In a study of febrile, gastrointestinal, and respiratory infections in Icelandic childcare, both season and age were consistent risk factors for all types of infection for childcare attendees. For each year a child aged between 2 and 6 years increased in age, the number of illness episodes they experienced decreased by 20%–50% (169). The protective effect of age against disease in children attending childcare is predominantly due to the cumulative build-up of immunity through prior infection; increased age as a protective factor due to more mature immune function is another possible factor.

Age-related differences in immune response can also be shaped by family structure and birth order. Those infants with older siblings tend to be exposed to a broader array of microbial antigens earlier in life, which may contribute to more rapid maturation of the immune system. For example, studies based on administrative or hospitalization data documented that prior to age 1, younger siblings are up to three times as likely to be hospitalized with infection-related conditions as older siblings (170, 171). Children build an increasingly diverse antibody and cellular immune repertoire, which is protective as they enter the school system.

There may be opportunities afforded by our increasing understanding of early childhood immunity to "fine-tune" the age at first infection, with some of the pathogens discussed here, or to immunize infants and children during the periods of greatest risk of severe outcomes. It is broadly recognized that some infections are linked to increased severity as age at primary infection increases (VZV [172]), while for others, it is highly desirable to delay the age at primary infection (RSV [173]). A greater understanding of how age at first infection is affected by childcare attendance could lead to changes in recommended vaccines and immunization schedules. For example, infants and children attending childcare settings during winter could be recommended passive immuniza-

tion with a monoclonal antibody such as nirsevimab to provide increased protection against RSV (174) after the waning of maternal antibodies.

CONCLUSIONS

Respiratory, gastrointestinal, and exanthematous illnesses in infants and young children are common and driven by a wide variety of viral and bacterial pathogens. Employers need realistic expectations about the likelihood and frequency of both child and parental/caregiver sickness absence following the end of parental leave. Attendance at formal childcare may tip the balance in favor of infection now rather than later.

Vaccination lowers the burden of disease morbidity and is currently our best tool for preventing or ameliorating childhood illnesses. Many countries are currently in a period of flux for RSV and VZV immunization strategies. The UK hopes that success from the current maternal RSV vaccination program can be built upon with increased uptake and that the success of the VZV vaccination program elsewhere in the world will be replicated and lead to improvements for UK children soon. Increased use of molecular diagnostics will better define the scale of the problem of childhood infections and allow prioritization of pathogens for future vaccine development to reduce morbidity.

Definitions

Throughout this article, we use National Health Service age definitions for infant and toddler (https://service-manual.nhs.uk/content/inclusive-content/age). Infants are under 1 year old. Toddlers are 1–3 years old. Childcare includes settings described as nursery, daycare, kindergarten, out-of-home childcare, and group childcare.

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AUTHOR AFFILIATIONS

[1]Baker Institute for Animal Health, Cornell University, Ithaca, New York, USA
[2]Department of Microbiology and Immunology, College of Veterinary Medicine, Cornell University, Ithaca, New York, USA
[3]UCL Genetics Institute, Department of Genetics, Evolution, and Environment, University College London, London, United Kingdom
[4]Division of Infection and Immunity, Institute of Immunity and Transplantation, University College London, London, United Kingdom
[5]North Middlesex University Hospital, Royal Free NHS Foundation Trust, London, United Kingdom
[6]Department of Genetics, University of Cambridge, Cambridge, United Kingdom

AUTHOR ORCIDs

Sarah L. Caddy http://orcid.org/0000-0002-9790-7420
Lucy van Dorp http://orcid.org/0000-0002-6211-2310
Leo Swadling http://orcid.org/0000-0002-0537-6715
Charlotte J. Houldcroft http://orcid.org/0000-0002-1833-5285

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AUTHOR CONTRIBUTIONS

Sarah L. Caddy, Conceptualization, Data curation, Writing – original draft, Writing – review and editing | Lucy van Dorp, Conceptualization, Data curation, Visualization, Writing – original draft, Writing – review and editing | Leo Swadling, Conceptualization, Data curation, Visualization, Writing – original draft, Writing – review and editing | Yuan Wis Wang-Koh, Conceptualization, Data curation, Writing – original draft, Writing – review and editing | Charlotte J. Houldcroft, Conceptualization, Data curation, Visualization, Writing – original draft, Writing – review and editing

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AUTHOR BIOS

Sarah L. Caddy is an Assistant Professor at the Baker Institute for Animal Health, Cornell University, USA, and an expert in viral immunity with a particular focus on maternal antibodies. Sarah trained in the UK at the University of Cambridge, Imperial College London and the MRC Laboratory of Molecular Biology. She began her independent research program as a Wellcome Trust Clinical Research Career Development Fellow in 2019, before relocating her laboratory to Ithaca, New York, in 2022. Her research explores how immune protection against viral infection is generated and transferred, with an emphasis on understanding how antibodies induced by enteric infection or vaccination protect infants during early life. She investigates host–virus interactions and the mechanisms mediating antibody transfer during pregnancy and breastfeeding, aiming to inform improved neonatal and maternal immunization strategies.

Lucy van Dorp is a UKRI Future Leaders Fellow and Principal Research Fellow in Microbial Genomics at UCL Genetics Institute, University College London, UK. She completed her PhD in human population genetics, working with ancient and modern human data, before moving into microbial genomics, where she applied population genetic approaches to modern bacterial genomes to investigate the drivers of diversity in major hospital-associated pathogens. In 2020, she was awarded a UCL Excellence Fellowship, after which she played a central role in the genomic analysis of SARS-CoV-2 during the COVID-19 pandemic, contributing to understanding viral evolution and transmission at scale. In recognition of her work, she received the Genetics Society's Balfour Lecture in 2023 for outstanding contributions to genetics by an early career investigator. She is a group leader in microbial genetics at UCL, where her research develops evolutionary and genomic approaches to infectious disease epidemiology across both ancient and contemporary timescales.

Leo Swadling is an Associate Professor in the Infection and Immunity division at University College London, UK, supported by a Wellcome Trust Career Development Award, UKRI DPFS and the Rosetrees trust. He did his PhD at the University of Oxford, developing genetic and molecular technologies to optimise T-cell vaccines for hepatitis C (Profs. Ellie Barnes and Paul Klenerman). He moved to London to study tissue-residency with Prof. Mala Maini. During the COVID-19 pandemic he characterised SARS-CoV-2-specific immunity as part of UK-CIC (www.uk-cic.org/) and COVIDsortium (covid-consortium.com/). This work helped to identify a role for T-cells in early aborted infections, and the protective role of pre-existing cross-reactive memory T-cells. He established the 'T-cell vaccines lab' at UCL in 2022, which aims to identify T-cell correlates of protection, through integrating studies of T-cell quality (function, phenotype, trafficking) and specificity (virus, protein, epitope, TCR clonality) and to rationally design vaccines to recapitulate these correlates.

Yuan Wis Wang-Koh is a Specialty Registrar in Emergency Medicine at the North Middlesex University Hospital, London, UK. She completed her pre-clinical [BA (Hons)] and clinical (MB, BChir) studies at the University of Cambridge and is currently finishing her training in Emergency Medicine in the North East Central London deanery. She recently completed a Diploma in Child Health from the Royal College of Paediatrics and Child Health. Wis also undertook undergraduate research on the genetics of bdelloid rotifers in the laboratory of Prof. Gos Micklem (Department of Genetics, University of Cambridge).

Charlotte J. Houldcroft is an assistant professor in the Department of Genetics, University of Cambridge, UK. She completed her PhD at the Wellcome Sanger Institute in the laboratory of Prof. Paul Kellam, studying the impact of human genetic variation on control of Epstein-Barr virus latency. Subsequently, she has worked on the genomics of DNA virus infections in immune compromised children (UCL Institute of Child Health, Prof. Judith Breuer), and the T cell immunology of cytomegalovirus control in solid organ transplant recipients (University of Cambridge, Prof. Mark Wills). Her virus genomics group at Cambridge researches DNA viruses from global health, genomic and immunological angles, including the pandemic potential of adenoviruses. Charlotte is also passionate about how ancient DNA can transform our understanding of the transmission and evolution of common human viruses in deep time.