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Risk analysis for outpatient experimental infection as a pathway for affordable RSV vaccine development

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Controlled human infection models (CHIMs) are an important tool for accelerating clinical development of vaccines. CHIM costs are driven by quarantine facilities but may be reduced by performing CHIM in the outpatient setting. Furthermore, outpatient CHIMs offer benefits beyond costs, such as a participant-friendly approach and increased real-world aspect. We analyze safety, logistic and ethical risks of respiratory syncytial virus (RSV) CHIM in the outpatient setting. A review of the literature identified outpatient CHIMs involving respiratory pathogens. RSV transmission risk was assessed using data from our inpatient and outpatient RSV CHIMs (EudraCT 020-004137-21). Fifty-nine outpatient CHIMs using RSV, *Streptococcus pneumoniae*, rhinovirus, and an ongoing *Bordetella Pertussis* outpatient CHIM were included. One transmission event was recorded. In an inpatient RSV CHIM, standard droplet and isolation measures were sufficient to limit RSV transmission and no symptomatic third-party transmission was measured in the first outpatient RSV CHIM. Logistic and ethical advantages support outpatient CHIM adoption. We propose a framework for outpatient RSV CHIM with risk mitigation strategies to enhance affordable vaccine development.

Respiratory syncytial virus (RSV) is a major cause of illness and death worldwide, primarily affecting children under the age of five in low- and middle-income countries (LMICs)[1]. In older adults (>60 years) RSV burden is estimated to be similar to that of seasonal influenza[2]. Recently an extended half-life monoclonal antibody, nirsevimab, has been approved for prevention in infants[3]. However, future use of this intervention will likely be limited to high-income countries due to drug costs[2], which highlights the problem of global therapeutics inequity. The first maternal RSV vaccine has been approved by the FDA. RSV preF vaccine has been shown to reduce medically attended RSV lower respiratory tract disease incidence in infants[4], but is not yet widely available. While limited resources and inadequate infrastructure for implementation of immunization interventions contribute to this immunization gap, the most substantial barrier to immunization access is high costs[5]. As populations in LMICs face the highest burden of mortality from vaccine-preventable diseases, such as RSV[6], there is an urgent unmet need for affordable RSV prevention.

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Controlled human infection models (CHIMs) have the potential to accelerate vaccine and anti-viral therapeutics development by rapid and affordable safety and efficacy testing and potentially prevent costly failures in late-stage trials[7]. Not only can CHIM be used for early proof-of-concept to test therapeutics efficacy, but it can also offer the potential to better understand protective immunity, improve vaccine design and delivery, de-risk therapeutics development for complex pathogens, and allow rapid vaccine adaptation in the case of antigenic drift[8]. CHIMs have provided valuable data in the development of vaccines for various diseases, including typhoid[9], shigella, influenza, dengue, and malaria[7]. The malaria vaccine (RTS,S/AS01 and R21/Matrix-M) is an example of the use of CHIM for proof-of-concept and the vaccine is now in the process of being implemented in LMICs[10,11]. However, the role of CHIM in licensure is not specific to outpatient CHIMs (as compared to inpatient CHIM) as no additional regulatory advantages are expected from conducting CHIMs in an outpatient setting.

Despite the potential of CHIMs to accelerate vaccine development, the high cost of quarantine facilities with dedicated staff limits widespread use. Outpatient CHIMs may further decrease trial costs, aligning with the goal of affordable vaccine development. While several RSV CHIMs have successfully been conducted in the inpatient setting[8], there is no evidence-based framework for RSV CHIMs in the outpatient setting. Here, we aim to assess safety, logistic and ethical considerations of outpatient RSV CHIMs in order to provide a framework for future RSV outpatient CHIMs to support the development of affordable preventative and therapeutic strategies.

Results

Review: included studies

Altogether, 59 outpatient CHIM studies with a total of 2789 participants were included (Fig. 1) in the systematic review. Six interviews and three questionnaires were completed with corresponding authors for 41/59 of the included studies. Data from 59 studies were extracted (Fig. 2 and Supplementary Table 3) and three different respiratory pathogens were identified (44 rhinovirus studies with 1774 participants, 14 *Streptococcus pneumoniae* studies with 966 participants and one RSV study with 49 participants). Additionally, data regarding safety were collected from two ongoing outpatient trials for *Bordetella Pertussis (B. Pertussis)* identified through the interviews. Two studies were partially outpatient: (1) an RSV CHIM in which participants resided at home for the first three days and stayed at a quarantine unit for the remainder of the study on the basis of expected viral shedding[12] and (2) a *Streptococcus pneumoniae* pilot trial conducted in Malawi in which inoculated participants remained at the clinic for the first three days, as this period posed the greatest risk of disease manifestation[13].

Review: safety

We examined safety risks of outpatient CHIM studies by collecting data on third-party transmission, PPE usage, inoculation, participant transportation, and emergency care provision. No studies (0/59) implemented home quarantine measures. Various strategies, such as the exclusion of volunteers who reside with at-risk individuals, were implemented to limit third-party

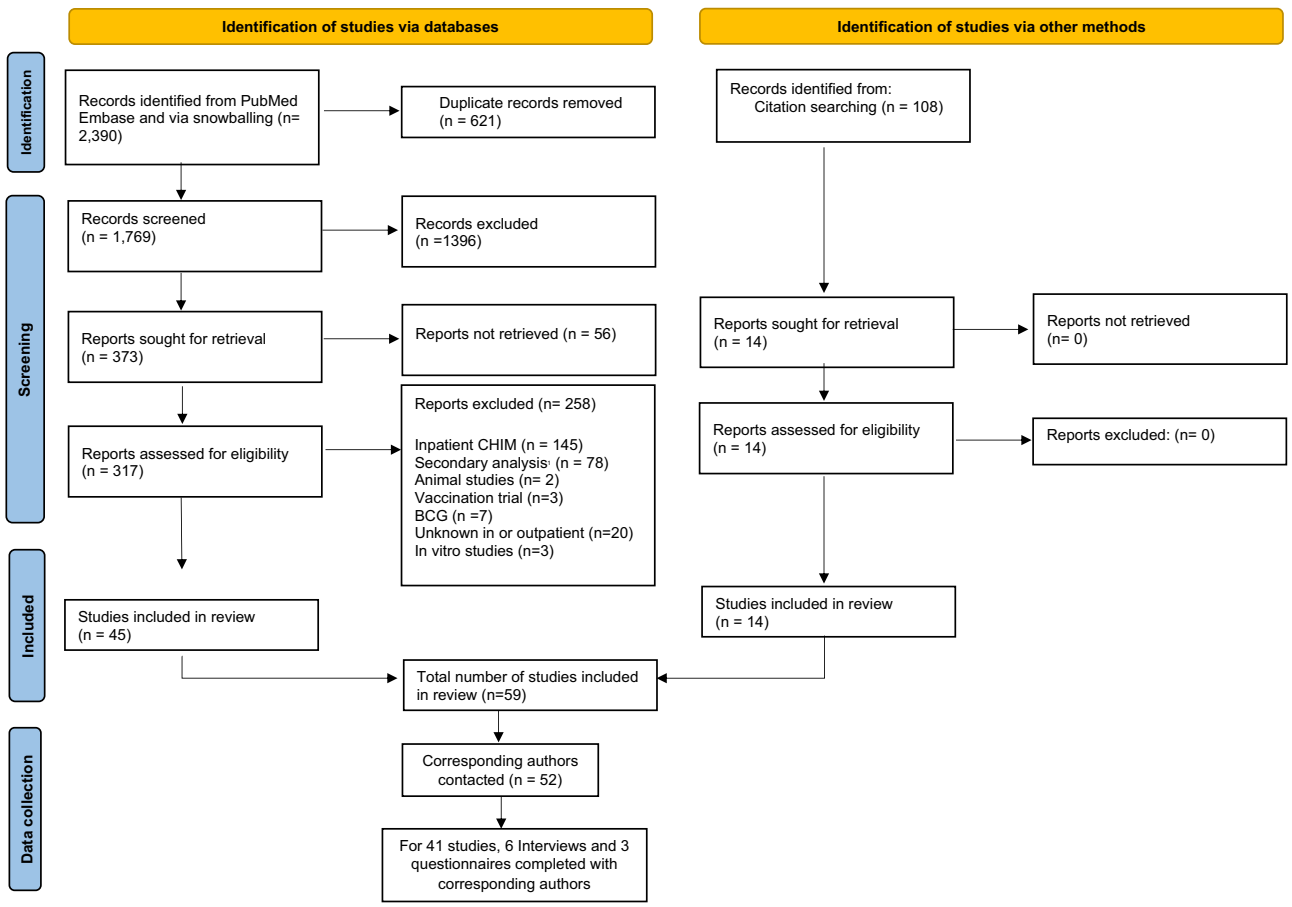

Fig. 1 | Flowchart study selection and data collection. Preferred reporting items for systematic reviews and meta-analyses (PRISM) flow diagram. The search yielded 2390 records, of which 621 duplicates were removed. Based on title- and abstract screening 1396 records were excluded. In total, 58 reports were not retrieved (14 with no full text available and 44 conference abstracts). Authors of conference abstracts were contacted to identify eligibility and availability of full text articles after which no additional reports were included. In total, 254 reports were excluded for various reasons, the majority due to an inpatient trial setting. For 20 records the study setting remained unknown after contacting authors, and records were excluded. Fourteen studies were included through snowballing via a list provided by the authors of included studies, detailing their published CHIM studies. In total, 52 corresponding authors were contacted and for 41 of the included studies, six interviews, and three questionnaires were completed.

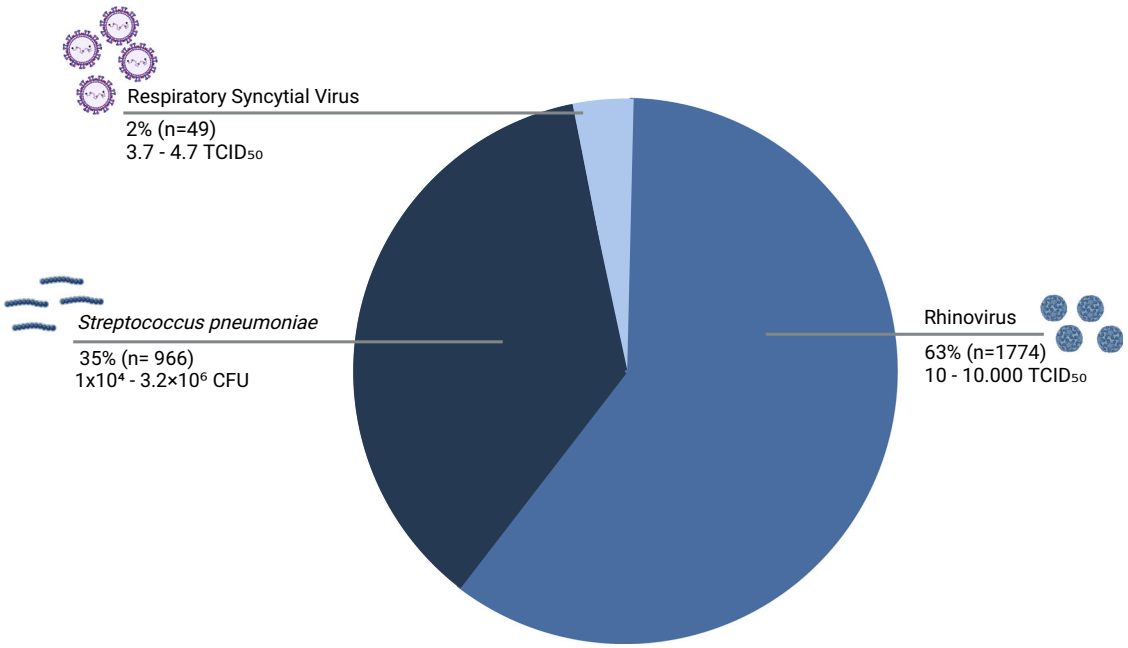

Fig. 2 | Outpatient and partially outpatient respiratory CHIM studies per pathogen. Pie chart of included studies per pathogen showing number of challenged participants, the percentage of participants out of the total number of participants who participated in outpatient respiratory CHIMs and the range of inoculation doses used. Two studies were partially outpatient: (1) an RSV CHIM in which participants resided at home for the first three days and stayed at a quarantine unit for the remainder of the study on the basis of expected viral shedding43 and (2) a *Streptococcus pneumoniae* pilot trial conducted in Malawi in which inoculated participants remained at the clinic for the first three days, as this period posed the greatest risk of disease manifestation.44 Two ongoing unpublished outpatient CHIMs using *B. Pertussis* were not included in this figure. Created in BioRender. Delemarre, E. (2025) https://BioRender.com/i14r556.

Table 1 | Overview of different measures taken to limit safety risks in outpatient respiratory CHIMs included in this review

Measures	
General	Personal hygiene and handwashing (Rhinovirus)
	Participants with housemates at risk of severe infection (i.e., immunocompromised) as exclusion criteria (Rhinovirus and *Streptococcus pneumoniae*)
	Insurance of health-costs for housemates in case of pathogen transmission for the duration of the study (*Streptococcus pneumoniae*)
PPE-usage	No use of PPE throughout the study (most common both in Rhinovirus and *Streptococcus Pneumoniae*)
	Surgical facemasks by participants during inoculation and study visits in the hospital (Rhinovirus)
	Gloves and surgical facemask by staff solely during inoculation (Rhinovirus)
	Disposable gowns and surgical facemasks for staff and participants during inoculation and sample collection (*Streptococcus pneumoniae*)
Transportation of participants	No restriction regarding transportation post-inoculation (most common in both Rhinovirus and *Streptococcus pneumoniae*)
	Instructions for participants to use facemasks when commuting home after inoculation (Rhinovirus)
	Participants were instructed not to take public transportation when symptomatic infection was present (Rhinovirus)
	Facemasks when commuting to the clinic (Rhinovirus)
Providing emergency care	Round-the-clock accessibility of study staff via telephone (rhinovirus and *Streptococcus pneumoniae*)
	Emergency study visits arranged at the participants' residence or at the study site (rhinovirus and *Streptococcus pneumoniae*)
	The requirement for participants to reside within a ten-kilometer radius of the study hospital (*Streptococcus pneumoniae*)
	Instructions to participants to visit the emergency room for life-threatening emergencies (Rhinovirus and *Streptococcus pneumoniae*)
	Providing access to emergency medication for participants at home (such as prednisone for asthmatic participants or antibiotics in Streptococcus pneumoniae trials)

Measures are categorized by general, PPE-usage, transportation of participants, and providing emergency care. Pathogen used in the CHIM where the measure was implemented is specified between brackets.

transmission risk (Table 1). One rhinovirus study incorporated assessment of third-party transmission into the study protocol[14]. In this study, one transmission event occurred (1/42, 2.4%) to a household member, which resulted in mild upper respiratory tract symptoms. No other studies reported incidents of third-party pathogen transmission. The potential risk of third-party transmission was explained to participants before enrollment and most authors attributed the prevention of third-party transmission to participants' responsibility. One *Streptococcus pneumoniae* study requested signatures from the roommates of participants to indicate their consent to the potential risk of third-party transmission. Two outpatient trials[15] for *Bordetella Pertussis* are currently ongoing. One of these trials requires pre-consent in order to confirm that participants understand the risks of

participation in the trial. In both trials, a phased approach is used to transition from inpatient to outpatient trials including (1) collecting data on environmental shedding in an inpatient trial[16] (2) involving the national public health authority (3) enrolling bedroom-sharers in the outpatient setting to study transmission. It will be assumed that if there is no transmission to bedroom sharers then community dissemination is unlikely in a population with a high vaccination rate, broad circulation of *Bordetella Pertussis* and no contact with high-risk individuals. [Personal communications Robert Read & Dimitri Diavaopoulos].

Measures to ensure the provision of emergency care, PPE usage, and instructions for participants on commuting to the study site, varied across studies (Table 1). General PPE measures have increased since the COVID-19 pandemic, either due to increased awareness of infection risk or to prevent co-infection with SARS-CoV-2, regardless of the inoculum. In all outpatient studies the inoculation procedure was identical to inpatient CHIMs and was conducted at the study site. After inoculation participants returned to their natural living environment. Several incidents (i.e., participant became unwell or fainted ultimately attributed to a mild-viral co-infection) occurred during *Streptococcus pneumoniae* CHIMs for which emergency care was needed and care was provided through an emergency home visit or a telephone call to the study doctor. For these incidents, emergency care could be provided sufficiently and the outpatient setting did not prove to be a barrier. However, difficulties were experienced in the potential ability to provide emergency care due to either participants traveling, which was against study protocol, or unreachability of participants. In the event of unreachability, the next of kin were contacted or study personnel visited the participants' homes to assess the situation.

In summary, key safety risks identified include third-party transmission and the ability to provide emergency care. Risk mitigation strategies using PPE and contact information are successful in limiting transmission and allowing for the timely provision of emergency care (Table 1, Fig. 4).

Primary data: safety—RSV transmission in an inpatient RSV CHIM

In our inpatient RSV CHIM, there were no instances of direct or indirect transmission of RSV. No infectious virus was detected on the most frequently contaminated fomites[17] in rooms of infected participants although genetic material was recovered [Supplementary Fig. 1]. The $TCID_{50}$ was below the limit of detection for all fomite samples before and after cleaning with alcohol (Fig. 3). Therefore, the pre-determined acceptance criterion of viral titer at least ten times lower than the titer needed for potential infection (2.2 Log_{10} 50% tissue culture infectious dose (TCID50))[18] was met. Genetic RSV material was measured using q-PCR on fomites, which was reduced through cleaning with alcohol (Supplementary Fig. 1) (for full results see supplementary materials). Furthermore, personnel in close contact with infected participants (performing inoculation and sample collection) tested negative ($n = 4$) for RSV indicating lack of direct RSV transmission when adhering to WHO droplet and isolation procedures. It should be noted that these results are based on transmission of the Memphis-37 strain, which is currently the most widely used RSV inoculum. Between 2010 and 2024, the Memphis37 challenge strain has been used 21 times, accounting for 100% of the conducted RSV CHIMs during this period. When using a different strain additional measures may be considered as third-party transmission risk should be reevaluated although in general pathogen-specific precautions are not strain-specific

Primary data: safety—RSV transmission in an outpatient RSV CHIM

In the first RSV outpatient CHIM, study participants reported 13 housemates with symptoms of respiratory tract infection during daily home visits. When household members of participants became symptomatic a single point-of-care (POC) test was performed from study day 6 onward. Five of these reports met the criteria for a potential transmission event and were tested for RSV; all (5/5) tested negative for RSV [Supplementary Fig. 3]. Eight housemates with respiratory symptoms were not tested as their symptoms did not correspond to a potential transmission event (symptoms started before day six ($n = 6$), study participant was RSV-negative ($n = 1$) or no contact between study participant and housemate ($n = 1$). In summary, there was no symptomatic RSV transmission to household members in the first global RSV outpatient CHIM.

Review: logistics

According to author interviews, study costs of outpatient CHIMs were considerably lower than those of inpatient CHIMs. Inpatient CHIM costs are driven by rental of the quarantine unit (estimated based on an average CHIM protocol at 35,000 euros per participant), round-the-clock study staff, participant facilities (e.g., food), and higher participant compensation in the inpatient setting. Costs specific to the outpatient setting may be associated with home visits and sample transport to the lab.

In most of the included studies (58/59), participants commuted to the study site for sample collection and in all studies participants were compensated for transportation costs (e.g., taxi or fuel costs). Home sampling was utilized for selected samples if self-sampling was feasible (i.e., nasosorption[19] and nasal-swab) and if samples did not require immediate processing (i.e., nasal lavage)[20]. Home samples were stored in the freezer until collected by research staff. No difficulties with home sampling were experienced and a high compliance rate was achieved

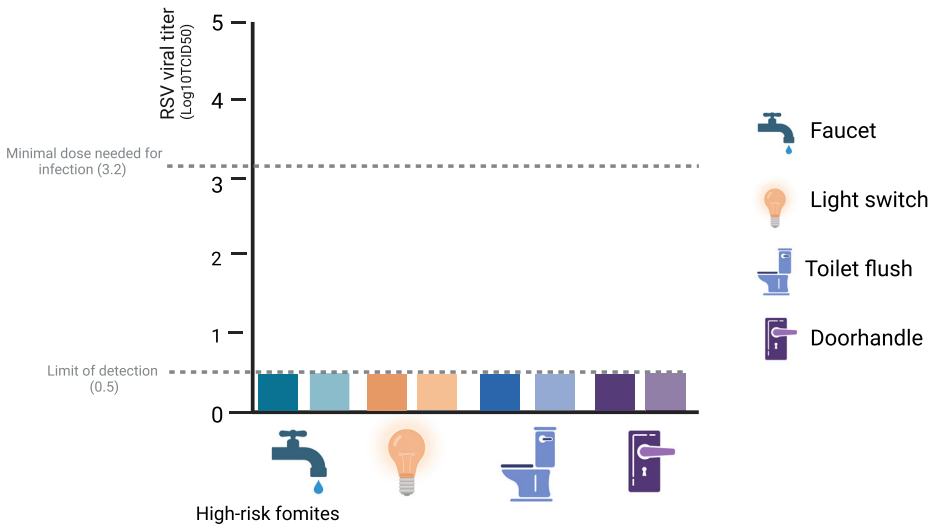

Fig. 3 | RSV transmission via high-risk fomites before and after cleaning with alcohol in quarantine rooms of RSV-positive participants. Respiratory syncytial virus (RSV) recovered from high-risk fomites was measured via viral titration (RSV viral titer). Viral titration (*Y*-axis) was measured in Log10 TCID50, with a limit of detection of 0.5 Log10 TCID50 and a previously established[18] minimal dose needed for infection of 3.2 Log10TCID50. Samples were taken from high-risk fomites including faucet, light switch, toilet flush and doorhandle (shown from left to right on the *X*-axis). Samples were collected from the rooms of all RSV+ participants, above shows the median and interquartile range of all the samples per fomite. Dark colors indicate the samples taken before fomite cleaning with 70% ethanol, while light colors represent samples taken after fomite cleaning. Created in BioRender. Delemarre, E. (2025) https://BioRender.com/b08z113.

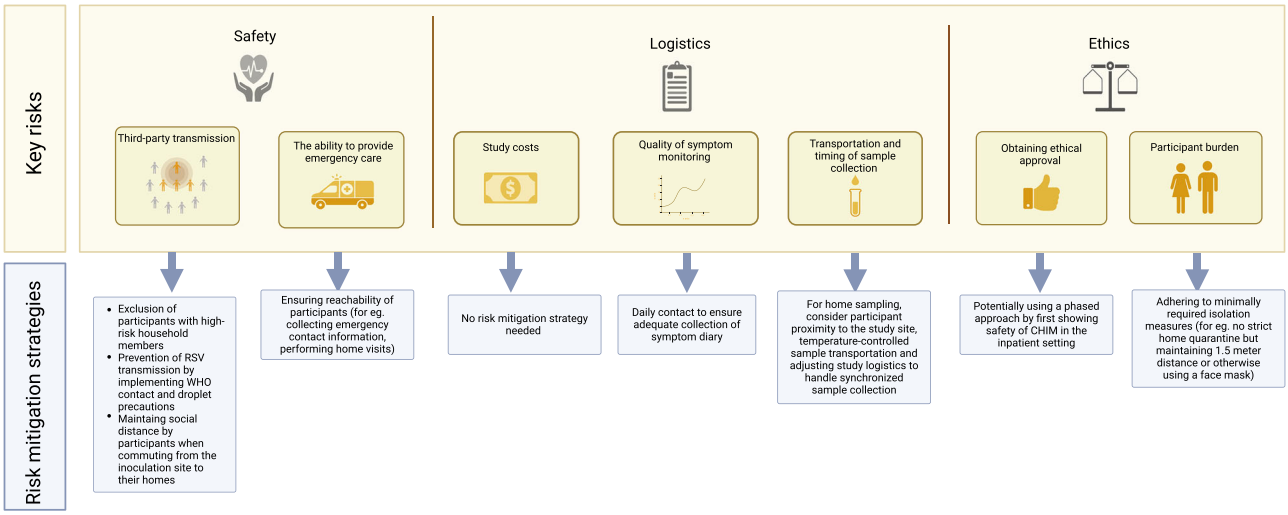

Fig. 4 | Key safety, logistic, and ethical risks of outpatient respiratory CHIMs and proposed risk mitigation strategies for RSV outpatient CHIM. Key risks regarding safety (third-party transmission and the ability to provide emergency care), logistics (study costs, quality of symptom monitoring and transportation and timing of sample collection) and ethics (obtaining ethical approval and participant burden) are shown in the top row. For each risk a corresponding risk mitigation strategy for an outpatient RSV CHIM is proposed. Created in BioRender. Delemarre, E. (2025) https://BioRender.com/n07n656.

(96.8%)[20]. Risks of home sampling include non-synchronized sample collection times causing diurnal fluctuations of samples, increased time until sample processing, fluctuations in sample temperature during transport, suboptimal sample collection conditions in participants homes, and inadequate collection technique when not observed by study staff (in case of self-sampling). However, home collection offers the advantage of reducing participant burden and further minimizing the potential risk of third-party transmission. In the included studies, symptom monitoring was done by self-reported symptom diaries, telephone contact, and clinical evaluations during site visits. Clinical evaluations enhance the quality of symptom monitoring as symptoms are objectified by study staff.

Another advantage of outpatient CHIMs is that it may aid recruitment. Ease of recruitment may be further enhanced due to the COVID-19 pandemic, in which home quarantine and the use of PPE have become more familiar and acceptable to the general public.

In summary, key logistic risks identified were study costs, quality of symptom monitoring, and logistics of sample collection (Fig. 4). Implementing risk mitigation strategies effectively results in minimal logistic risks for outpatient RSV CHIMs.

Primary data: logistics of first global RSV outpatient CHIM and inoculation stress test

In the first global outpatient RSV CHIM risk mitigation strategies were used to minimize logistic challenges. The majority of study participants resided within a ten-kilometer radius of the study site allowing for a minimal time from sample collection to sample processing. Inoculation was performed at the study site instead of the home setting as we observed that the viral titer of RSV-A Memphis 37b stored on wet ice drops ~1 log TCID50 every 30 min [Supplementary Fig. 2]. The stress test of the RSV-A Memphis 37b inoculum stored on wet ice showed a mean titer of 1×10^4 TCID50/ml after 15 min and 3, 16×10^3 TCID50/ml after 30 min compared to 4, 21×10^4 TCID50/ml before storage at $t = 0$ [Supplementary Fig. 2]. Thus, the titer of the inoculum was sufficiently stable for a maximum of 15 min stored on wet ice, which prohibited inoculation during home visits and supported the choice to inoculate at the study site. Coordination of home visits and laboratory processing was logistically more challenging than in the inpatient setting or than outpatient CHIM where sample collection occurred at the study site. The majority of sample collection was performed during home visits to minimize the burden for study participants.

Review: ethics

In general, there were no insurmountable ethical challenges in obtaining ethical approval specific to outpatient based CHIM studies. However, some research groups initially experienced difficulties due to the possible risk of third-party transmission. To obtain ethical approval, it was argued that the pathogen used is a common circulating pathogen and therefore the added risk of circulation due to CHIMs is negligible. Furthermore, because of general circulation of the pathogen amongst the population there is considerable population immunity and therefore a significantly decreased risk of causing an outbreak. Respiratory CHIM in higher-risk participants, such as patients with asthma or chronic obstructive pulmonary disease, raised safety concerns for the institutional review board. Safety of a CHIM in these selected high-risk groups was first shown in the inpatient setting with HRV[21]. Later, researchers were able to demonstrate the safety of outpatient CHIM studies by either conducting pilot studies or by slowly building a track-record of conducting safe CHIMs[22]. For high risk RSV populations, safety of CHIM has been demonstrated in the inpatient setting in older adults[22].

In medical research, there is an ethical imperative to minimize the research burden to participants wherever possible. We examined the acceptability of participant burden in the outpatient setting. All authors noted that compared to inpatient CHIMs, the study burden on participants in the outpatient setting is significantly reduced because there is no need for inpatient quarantine, which is disruptive to participants lives. By adhering to minimally required isolation measures in the outpatient setting, participant burden can be further reduced. One research group conducted an acceptability study and found that participants perceived the study burden to be low in the outpatient setting[23].

Another advantage of outpatient CHIM studies is increased generalizability of results because participants remain in their regular living conditions, exposed to the same environmental conditions, pathogens and environmental factors, such as air quality, allergen exposure, and behavioral routines as they would in their everyday lives. Furthermore, outpatient CHIMs are more participant friendly making recruitment easier and faster, and make more widespread possibility to conduct RSV CHIM as availability of an inpatient quarantine capacity is not a limiting factor[24]. On the other hand, the outpatient setting is a less controlled setting making it more difficult to identify results in a smaller group due to potential increased variability. In addition to these benefits, a clear ethical advantage of outpatient CHIMs is that by further reducing costs it has the potential to contribute to global vaccine equity. Furthermore, there is an ethical

imperative to avoid restricting participants' freedoms via quarantine if there is no scientific or public health reason to do so. In summary, key ethical risks of outpatient CHIM include not obtaining ethical approval and acceptability of participant burden [Fig. 4]. Other potential ethical considerations that could be made are the possibility to treat or manage third-party transmission events, consequences of third-party transmission, pathogen survival outside the host and mode of transmission.

From an ethics perspective, a risk is comprised of the chance of the event happening and the consequences of the event ("impact"). For a framework to assess risks related to outpatient CHIMs see Supplementary Table 4. Primary data on ethics from our outpatient CHIM are listed in supplementary note 4.

Discussion

Our review showed that respiratory outpatient CHIMs pose a minimal safety risk. Analysis of fomite swabs from our inpatient CHIM, and historical studies in the outpatient setting support a negligeable risk of RSV transmission via indirect contact. Additionally, the risk of transmission through other routes, such as droplets or small-particle aerosols, is low given that RSV transmission is primarily driven through self-inoculation after touching contaminated surfaces[25]. Furthermore, as viral load during RSV infection of healthy young adults with mild URTI is low, airborne transmission risk is likely lower in this population. Hence, the probability of a transmission event occurring is minimal, though not entirely eliminated so participants with high-risk household members should be excluded. Furthermore, we show that logistic risks related to inoculation, sample collection, or reliability of symptom monitoring can be adequately mitigated and ethical advantages outweigh ethical risks. A major strength of this study is the systematic nature in which RSV transmission was studied in the outpatient setting.

Unfortunately, as a fully outpatient RSV CHIM has never been conducted previously, we performed our risk analysis based on the best available evidence from other respiratory pathogens. Although some of our conclusions are based on rhinovirus and *Streptococcus pneumoniae* CHIMs, we believe that extrapolation to RSV can be made and that these data provide a conservative estimate of risks for RSV based on a comparison between these pathogens and RSV (Supplementary Table 5). In short, both RSV and rhinovirus are common circulating viruses[26,27]. High-risk populations for all three pathogens include young children and the elderly[28–33]. Rhinovirus significantly contributes to lower respiratory infections in children and adults[32,34–36], with potential higher morbidity and childhood asthma risk than RSV[36,37]. Furthermore, estimates of *Streptococcus pneumoniae* under-five mortality are higher than for RSV[33,38]. Additionally, rhinovirus may have higher transmissibility then RSV[25,39–41]. To put this into perspective, RSV is potentially less pathogenic and less transmissible than rhinovirus, a challenge agent, which has been used safely in the outpatient setting. To further evaluate overall transmission risk, as mentioned under ethics, a risk is comprised of the chance of the event happening and the consequences of the event ("impact"). If RSV is less pathogenic, the impact of third party transmission is less severe and if transmissibility is lower, the chance of an event happening are lower making the overall transmission risk lower for RSV outpatient CHIMs than rhinovirus outpatient CHIMs.

Our findings can be translated into risks and risk mitigation strategies for outpatient RSV CHIM trials (Fig. 4). To ensure safety and to prevent RSV transmission in the outpatient setting, we recommend adherence to the WHO contact and droplets precautions regarding PPE and quarantine measures[42]. For participants we recommend flexible quarantine with facemasks or social distancing of 1.5 m as a risk mitigation strategy. Importantly, the impact of transmission risk can be mitigated using exclusion criteria for participants who have contact with and/or have household members belonging to high-risk populations (children <3 years of age, adults >65 years of age and people with significant acute or chronic medical illness associated with an increased risk of respiratory viral illness related complications). Furthermore, conducting outpatient CHIMs outside the RSV season reduces the risk of transmission of non-challenge RSV from the general public to study participants increasing the scientific quality of the study. To minimize the potential risks of home sample collection, we recommend implementing inclusion criteria to limit the distance between participants' residences and the study site, using temperature-controlled sample transportation, and utilizing either a large study team or limiting the size of a cohort to allow for synchronized sample collection to prevent fluctuations in results.

A limitation of our primary data is that during our inpatient RSV CHIM we assessed viral load and RSV infectivity on fomites on day seven post inoculation (dpi), while participants median peak infectious viral load was measured on day four dpi. Therefore, the viral shedding on fomites is potentially underestimated. We expect the impact on study results to be limited because 4/5 (80%) of RSV + participants sustained high viral loads by quantitative polymerase chain reactions (qPCR) ($>10^8$ copies/mL) on day seven dpi. Furthermore, our transmission data is based on a single inpatient RSV CHIM, and involves a small sample size ($n = 6$). A limitation of the transmission study in the outpatient RSV CHIM is that asymptomatic RSV infections of household members and subsequent transmission were not included in our definition of a potential RSV transmission event. Due to feasibility and burden to household members, we decided to focus only on symptomatic transmission as this is most relevant for assessing third party risk according to the proposed risk assessment framework (Supplementary Table 4). However, the probability that asymptomatic third-party transmission will have a significant impact, such as causing severe disease, is low. By definition, an individual who acquires an infection through third-party transmission and remains asymptomatic does not exhibit clinical illness, thereby minimizing the impact of that transmission event. Consequently, the failure to detect such transmission events is of lesser concern. Furthermore, as individuals with asymptomatic infections do not exhibit respiratory symptoms, such as coughing or sneezing, the risk of RSV transmission in these cases is considered lower than symptomatic patients[43,44].

Due to unreachability of corresponding authors, additional information through interviews or questionnaires was not obtained for some included studies (18/59). This could create a potential information bias. However, we expect this effect to be minimal, as multiple pathogens were represented with no group being overrepresented. Nevertheless, the majority (41/59; 70%) of corresponding authors in the included studies provided additional information, minimizing the potential impact on our results. In addition, 23.7% (14/59) of the included studies were identified through snowballing, indicating that eligible studies may have been missed. The creation of an all-encompassing search term was challenging due to inconsistent terminology associated with CHIMs and the outpatient setting. We believe the possibility of missed trials to be limited, considering that we supplemented the search by utilizing the HIC-Vac network, an international consortium of CHIM investigators (https://www.hic-vac.org/) requesting their collaboration in providing any available outpatient CHIM studies within their knowledge. Furthermore, adenovirus CHIMs were not included as we selected pathogens for inclusion based on a recent systematic review of all CHIMs[42]. Furthermore, systematic measurement of transmission was often lacking, potentially resulting in missed instances of transmission.

Outpatient RSV CHIMs provide clear ethical advantages driven by reduced patient burden and the contribution to global vaccine equity. Our findings offer a framework by which outpatient CHIMs can be conducted safely and effectively, providing guidance for researchers and ethics committees, that will assist in the development of more rapid and affordable clinical trials.

Methods

Review

In this paper, we distinguish secondary data collected from our literature review from primary data collected during clinical trials. A systematic search was conducted on December 9, 2022 in the PubMed and Embase databases for studies on CHIM in the outpatient setting using respiratory pathogens. Respiratory pathogens from a recent systematic review on CHIM were

included[45]. For the full search terms see Supplementary Table 1. Additional relevant references were collected through snowballing (citations from included manuscripts). Studies were selected according to predefined inclusion and exclusion criteria (Supplementary Table 2). Studies using live-attenuated strains, such as the cold-adapted influenza vaccine or BCG, were excluded as, under regular conditions, these inocula do not cause disease in infected participants and therefore were not considered a respiratory pathogen. In 39 selected studies the study setting (outpatient or inpatient) was not evident from the abstract and corresponding authors were contacted to determine the design of the study. Titles, abstracts, and full texts were screened for study selection by two independent authors (EZS and JMHS) using the web application Rayyan[46], and data was extracted (Supplementary Table 3). Subsequently, corresponding authors were contacted and asked to either fill in a standardized questionnaire or set up an interview for additional data extraction on study outcomes (Supplementary Note 5). Outcomes on safety, logistics, and ethics were summarized and results from interviews were pooled. Through interviews with corresponding authors we identified two ongoing *B. Pertussis* outpatient CHIM trials for which corresponding authors were contacted and information regarding safety and transmission was obtained. Figures and tables were created with BioRender.com.

Primary data: RSV transmission in an inpatient RSV CHIM

In August and September 2022, we conducted an inpatient RSV CHIM study (EudraCT number 020-004137-21) in six healthy adult volunteers at the University Medical Center in Utrecht, the Netherlands. Ethical approval was obtained (NL78591.041.21). We measured the risk of RSV transmission, both directly and indirectly (via fomites). Study personnel adhered to standard droplet isolation PPE requirements (Supplementary Note 2). Research personnel with close contact with participants were tested for RSV by nasal swabs on day seven dpi by an RSV molecular POC test (GeneXpert®, Cepheid, CA, USA). On seven dpi, the expected day of peak viral load[47], swabs were taken from known high-risk fomites[17] in the rooms of all RSV positive (RSV positivity was determined based on cycle threshold (Ct) values bellow 45) study participants (5/6) (faucet, toilet flush handle, doorknob, and light switch). Samples were taken before and after cleaning with 70% ethanol. qPCR were performed as previously reported[48]. For viral culture assays fomite samples were plated onto 96-well tissue culture plates to determine viral titers. Each underwent quadruplicate ten-fold dilution series. 50 µl of each dilution was added to HEp-2 cell monolayers (60% confluence) in 50 µl/well DMEM supplemented with Normocin (100 µg/ml) and 1% fetal bovine serum. RSV quantitative standards were included in parallel. The standards were obtained from RSV-A supernatant grown in HEp-2 cells and stored at −80 °C in 25% Sucrose (final concentration). Cytopathic effects were assessed visually using light microscopy over 10 days. The viral titer was determined as the 50% TCID50 per mL using the Spearman–Kärber method[49]. The viral titration assay had a limit of detection of 0.5 Log_{10} TCID50.

The acceptance criterion for adequate RSV prevention was pre-defined as a viral titer ten times lower (2.2 Log_{10} 50% TCID50) than the titer needed for infection in intranasally inoculated adults (3.2 Log_{10}TCID50) from the fomite samples after cleaning with 70% ethanol[18].

Primary data: RSV transmission in an outpatient RSV CHIM

From October through December 2023 we performed the first outpatient RSV CHIM globally (EudraCT number 020-004137-21). Ethical approval was obtained (NL78591.041.21) and full methods of the study can be found in the supplementary materials. Participants in the first outpatient RSV CHIM were instructed to self-quarantine for 10 days unless they tested negative for RSV on day seven. Self-quarantine measures included keeping 1.5 m distance from others and use of a face mask when social distancing was not possible. There was no strict home quarantine and participants were allowed to pursue daily activities, such as attending classes and doing groceries at the supermarket. Study personnel inquired daily whether household members showed signs of respiratory tract infection at each home visit. Housemates who showed any symptoms of respiratory tract infection were RSV POC tested immediately if the symptoms met the criteria for a potential transmission event. A potential transmission event was defined as symptoms that started at the earliest on day six after inoculation and the study participant tested positive for RSV. Asymptomatic household members where not tested.

Primary data: inoculation stress test

The stability RSV-A Memphis 37b was determined after storage on wet ice for different lengths of time (0–360 min) using the TCID50 assay according to the Spearman and Karber method[50,51]. The same dilution of virus was prepared as used for viral inoculation (10^4 plaque-forming units/mL [PFU/mL]). Cells were checked daily for CPE and an end determination was made after 7–10 days. TCID50 was calculated according to the following formula: Log (TCID50/volume) = $X_0 - (d/2) + ((d/n) * \Sigma xt)$. The experiment was repeated twice and mean titer was calculated based on both experiments.

Inclusion and ethics

Trials from which these data were gathered were performed in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent prior to participation in the study.

Data availability

The data supporting the findings of this study are available within the paper and its supplementary information files. Additional data used and/or analyzed during the current study are available from the corresponding author upon request.

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Author contributions

E.Z. Siegal contributed to project administration, data collection, data analysis, and interpretation and writing. J.M.H. Schoevers participated in data collection, analysis and interpretation, review, and editing. J.

Terstappen, E.M. Delemarre contributed to writing, visualization, review, and editing. S. L. Johnston, L.F. van Beek, D. Bogaert, C. Chiu, D.A. Diavatopoulos, D.M. Ferreira, S.B. Gordon, F.G. Hayden, M.I. de Jonge, M.B.B. McCall, H.I. McShane, A.M. Minassian, P.J.M. Openshaw, A.J. Pollard, J. Sattabongkot, R.C. Read, A. Troelstra, A. Wilder-Smiith, and M. van Wijk. L.J. Bont contributed to review and editing of the manuscript. N.I. Mazur participated in supervision, conceptualization, writing the original draft, and review and editing of the manuscript.

Competing interests

P.J.M.O. has been a paid member of scientific advisory boards for GSK, Moderna, Janssen, Seqirus, Pfizer, Sanofi, AstraZeneca, and Icosavax and a co-investigator on EU IMI awards, RESCEU and PROMISE, investigating the impact of RSV disease in Europe. F.G.H. has participated on a Data Safety Monitoring Board or Advisory Board, has participated in DSMB committees for RSV antiviral (Enanta), COVID therapeutic (Cytodyn, Enanta), influenza vaccine (Vaccitech) and is a non-paid consultant on RSV antivirals (Pfizer, Enanta). N.I.M. and L.B. have received support for attending meetings and/or travel from the ResViNET Foundation. UMC Utrecht has received grants from AbbVie, AstraZeneca, The Bill & Melinda Gates Foundation, the Dutch Lung Foundation, The Gates Medical Research Institute, GSK, Janssen, Med-Immune, MeMed, Merck, Novavax, Pfizer, and Sanofi; has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AbbVie, Ablynx, Astrazeneca, Bavaria Nordic, GSK, Janssen, MabXience, MedImmune, MEDtalks, Merck, Moderna, Novavax, Pfizer, and Sanofi and Virology Education. L.B. is founding chairman of the ReSViNET Foundation. M.B.B.M. has served as (unpaid) Local Safety Monitor on two inpatient LPS challenge studies, as well as (unpaid) on the Safety Monitoring Committee of amongst others an outpatient *Loa loa* treatment trial. Furthermore, he is, and has been, PI or senior co-investigator on various outpatient Controlled Human Malaria Infection studies. A.J.P. is chair of the UK Department of Health's Joint Committee on Vaccination and Immunization, which advises the UK Government on vaccine policy including the use of immunization for prevention of RSV infection.

Additional information

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